Injectable Opioid Agonist Treatment

iOAT for Opioid Use Disorder

NATIONAL

CLINICAL GUIDELINE

CRISM-ICRAS
Canadian Research Initiative in Substance Misuse
Initiative Canadienne de Recherche en Abus de Substance

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Injectable opioid agonist treatment prescribers, pharmacists, and nurses

Injectable opioid agonist treatment care teams including psychologists, social workers, peer workers, addiction counsellors, case managers, team leaders, program managers, and other health care providers

Organizations that provide substance use disorder and addictions treatment and care

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About the Canadian Research Initiative on Substance Misuse

Funded by the Canadian Institutes of Health Research (CIHR), the **Canadian Research Initiative on Substance Misuse (CRISM)** is a national research consortium focused on substance use disorder, comprising four large interdisciplinary regional teams (nodes) representing British Columbia, the Prairies Provinces, Ontario, and Quebec/Atlantic. Each CRISM node is an expert network of research scientists, service providers, policy makers, community leaders, and people with lived experience of substance use disorder. CRISM's mission is to translate the best scientific evidence into clinical practice and policy change. More information about CRISM can be found at: www.crism.ca.

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Disclaimer for Health Care Providers

The recommendations in this guideline represent the view of the national guideline review committee, arrived at after careful consideration of the available scientific evidence and external expert peer review. The application of the recommendations in this guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the needs, preferences, and values of an individual patient, in consultation with that patient and their guardians(s) or family members (when appropriate), and, when appropriate, external experts (e.g., speciality consultation). When exercising clinical judgment in the treatment of opioid use disorder, healthcare professionals are expected to take this guideline fully into account while upholding their duties to adhere to the fundamental principles and values of the Canadian Medical Association Code of Ethics, especially: compassion, beneficence, non-maleficence, respect for persons, justice, and accountability, as well as the required standards for good clinical practice defined by relevant governing bodies within regional or local jurisdictions. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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This guideline is intended to give an understanding of a clinical problem and outline one or more preferred approaches to the management of the problem. This guideline is not intended as a substitute for the advice or professional judgment of a health care professional, nor is it intended to be the only approach to the management of a clinical problem. We cannot respond to patients or patient advocates requesting advice on issues related to medication conditions. If you need medical advice, please contact a local health care professional.

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Executive Summary

Opioid use disorder (OUD) is one of the most challenging forms of substance use disorder facing the health care system in Canada and a major driver of the recent increase in overdose deaths across the country. In 2018, at least 4,460 Canadians died from an opioid overdose, with 94% determined to be unintentional (accidental) overdoses. This represents a 48% increase in overdose deaths from 2016 and a 9% increase from 2017. The recent emergence of street fentanyl, carfentanil, and other highly potent synthetic opioids increasingly cut into heroin and other street drugs is a pressing public health concern that has contributed significantly to the overdose emergency. Fentanyl and other synthetic analogues were implicated in 73% of opioid-related deaths in Canada in 2018, compared to 67% in 2017 and 50% in 2016. Although pan-Canadian opioid-related deaths were not tracked prior to 2016, it is known that there were at least 655 deaths in which fentanyl was determined to be a cause or contributing cause between 2009 and 2014, compared to an estimated 3,256 deaths involving fentanyl or fentanyl analogues in 2018 alone.

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. Injectable opioid agonist treatment (iOAT) is an evidence-based, high intensity, cost-effective treatment option for OUD for those patients who have not benefitted from other treatments and those whose individual situations and needs indicate they may benefit from injectable opioid agonist treatment.

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 (SROM) for a variety of reasons, including side effects, cravings persisting despite optimal oral opioid agonist treatment (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 guideline recommends that iOAT should be considered for individuals with severe, treatment refractory opioid use disorder and ongoing illicit injection opioid use; that both diacetylmorphine and hydromorphone may be appropriate treatment options; and that iOAT should be provided as an open-ended treatment, with decisions to transition to oral OAT made in collaboration with the patient.

The Canadian Research Initiative in Substance Misuse (CRISM), a Canadian Institutes of Health Research (CIHR)–funded research network, assembled an expert interdisciplinary committee composed of 30 individuals, including representation from physicians, nurses, pharmacists, people with lived experience, researchers, and front-line staff. This clinical guideline was developed to provide three key clinical recommendations as well as clinical guidance on the provision of iOAT. Recommendations and clinical guidance are based on a structured literature review and clinical expertise. Its partner document, National Injectable Opioid Agonist Treatment for Opioid Use Disorder Operational Guidance, provides guidance on the implementation, operation, and evaluation of iOAT programs.

1.0 Introduction

This document provides a brief overview of the rationale for and evidence supporting the use of injectable opioid agonist treatment (iOAT) for the management of opioid use disorder (OUD) followed by in-depth clinical guidance for the provision of iOAT. Considerations from the literature and clinical experience in Canada and other jurisdictions are provided, offering a framework for how to build a clinical practice of iOAT. However, the unique nature of each person's situation requires clinical judgement in order to determine the best course of treatment.

National Injectable Opioid Agonist Treatment for Opioid Use Disorder Operational Guidance (iOAT Operational Guidance), a partner guideline to this clinically-focused document, provides guidance on implementing an iOAT program and operational considerations.

1.1 BRIEF OVERVIEW OF iOAT RATIONALE AND EVIDENCE

In 2018, at least 4,034 Canadians died from an opioid overdose, with 94% determined to be unintentional (accidental) overdoses.[a] This represents a 48% increase in overdose deaths from 2016 and a 9% increase from 2017.[1] The recent emergence of street fentanyl, carfentanil, 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. Contamination of street drugs is ongoing and progressive, with new agents such as benzodiazepine analogues being found in substances sold as opioids. Fentanyl and other synthetic analogues were implicated in 73% of opioid-related deaths in Canada in 2018, compared to 67% in 2017 and 50% in 2016.[1] Although pan-Canadian opioid-related deaths were not tracked prior to 2016, it is known that there were at least 655 deaths in which fentanyl was determined to be a cause or contributing cause between 2009 and 2014,[2] compared to an estimated 3,256 deaths involving fentanyl or fentanyl analogues in 2018 alone.[1]

a Epidemiological data and research literature often use the term "overdose" or "accidental overdose" to refer to fatal and non-fatal dose intolerances to both prescription and illicit opioids. In the context of the drug supply being contaminated with fentanyl and other highly potent synthetic opioids, fatal and non-fatal overdoses may be reasonably considered "poisonings", as the adulteration of the drug supply makes it difficult if not impossible to determine a safe dose without knowing the composition and strength of illicit opioids and other substances which may also contain highly potent synthetic opioids.

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 (OAT) has proven to be the most effective approach to reducing all-cause mortality in individuals with opioid use disorder[3] and harms associated with illicit opioid use, including morbidity and mortality.[4-8]

Individuals with severe opioid use disorder who inject opioids may not adequately benefit from oral OAT medications for a variety of reasons, including cravings persisting despite optimal OAT dosing, patients being unable to reach a therapeutic dose, insufficient improvements in health, social function, or quality of life, or opting not to initiate oral OAT (e.g., previous experience with oral OAT including intolerable reactions to specific medication[b] or insufficient reduction in craving and illegal drug use). Individuals who inadequately benefit from first-line medications, or whose circumstances and risks otherwise indicate that they may benefit from iOAT, like other individuals using illicit opioids, face significant risks, including premature death, non-fatal overdose, blood-borne infectious diseases (e.g., HIV and hepatitis C), violence, and arrest.[9,10] Meta-analyses have shown that, among individuals who are treatment refractory[c] to methadone, prescription injectable diacetylmorphine—administered under the supervision of trained health professionals in a clinic setting—is beneficial in terms of reducing illicit opioid use, premature treatment discontinuation (or "treatment drop-out"), criminal activity, incarceration, and mortality as well as improving overall health and social functioning.[11-14] In response to regulatory barriers limiting the provision of diacetylmorphine for the treatment of OUD in Canada, the SALOME (Study to Assess Longer-term Opioid Medication Effectiveness) trial compared injectable hydromorphone to injectable diacetylmorphine and found both medications, delivered in identical conditions, showed positive outcomes such as high retention rates (over 77% intention to treat [ITT]; over 92% per protocol [PP] analysis), reduction of street opioid use (from daily to a few days per month), and reduction in illegal activities.[13] A more in-depth review of evidence supporting iOAT for the treatment of OUD is available in Appendix 1.

In jurisdictions where diacetylmorphine is currently not available, or in patients where it is contraindicated or unsuccessful, hydromorphone provides an effective, licensed alternative.[13]

b Although side effects for opioids are a class effect, individuals may have different experiences on different opioid medications.

c It should be noted that there has been an intentional shift away from the use of "treatment refractory," as it may inadvertently perpetuate stigma against individuals with opioid use disorder. This document uses this term, when necessary, to reflect its use in the scientific literature. However, substance use disorders are known to be chronic, relapsing conditions which may require multiple treatment approaches across the lifespan, thus rendering such a term and concept otherwise moot.

1.2 DEVELOPMENT PROCESS

See Appendix 2 for details of the development process and review process.

1.2.i Intended Audience

The target audience of this document is iOAT prescribers, pharmacists, and nurses, however, there is clinical utility for other members of iOAT care teams, including psychologists, social workers, peer workers, addiction counsellors, case managers, team leaders, program managers, other health care providers, and organizations that provide substance use disorder and addictions treatment and care. Clinical and operational leads may find this document useful in informing the implementation of iOAT. Although this document is primarily written for clinicians and other health care providers, individuals with lived experience of opioid use disorder may wish to read all or part of the document to inform their understanding of treatment options. Additional materials intended for people who use drugs and materials for the general public are available on the CRISM website.

1.3 PURPOSE AND SCOPE

This guideline was created to provide a framework to assist with the clinical practice of iOAT. This includes recommended eligibility considerations; prescription of iOAT; titration, stabilization, and transitions off iOAT; conversion to alternate OAT; supervision of injection; and referral to ancillary services. This guideline does not include guidance on program implementation and other operational issues. Its partner document, iOAT Operations Guidance, provides an overview of potential models of care for this treatment and guidance on selecting the most appropriate model for each site; recommendations on prescriber and staff competencies; guidance on obtaining and preparing injectable medications; and guidance on implementing evaluation of iOAT programs.

This document should be understood as a living document, which will be updated by the National iOAT Clinical Guideline Committee 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 and its partner guideline.

2.0 Clinical Recommendations

This clinical guideline makes three key recommendations regarding the provision of injectable opioid agonist treatment. These recommendations were formulated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework, which was developed to provide a transparent and systematic approach for making clinical practice recommendations.[15] These three key recommendations are based on the existing literature on iOAT, including two systematic reviews and meta-analyses. The rest of the guidance in this guideline can be understood as clinical guidance informed by the existing literature and reached by consensus of the experts on the National Injectable Opioid Agonist Treatment for Opioid Use Disorder Clinical Guideline Subcommittee.

The GRADE approach rates evidence quality as high, moderate, low, or very low. Evidence quality can also be understood as certainty of evidence or confidence in the estimated effect size. Recommendations can be rated as either strong or conditional. More information on the GRADE system can be found in Appendix 2; the full recommendations and accompanying evidence summaries can be found in Appendix 3.

	Recommendation	Quality of Evidence	Strength of Recommendation
Injectable Opioid Agonist Treatment			
1.	Injectable opioid agonist treatment should be considered for individuals with severe, treatment-refractory opioid use disorder and ongoing illicit injection opioid use.	Moderate	Conditional
Medication Selection			
2.	For patients who are determined to be likely to benefit from injectable opioid agonist treatment, both diacetylmorphine and hydromorphone are acceptable treatment options.	Low	Strong
Treatment End Date			
3.	Injectable opioid agonist treatment should be provided as an open-ended treatment, with decisions to transition to oral OAT made collaboratively with the patient.	Low	Strong

3.0 Clinical Practice Guidance

Summary of Clinical Practice Guidance

General considerations	Individuals with severe opioid use disorder who inject opioids and have continued to experience significant health/and or social consequences who have not benefitted from previous attempts at oral opioid agonist treatment, or other circumstances and risks that indicate they may benefit from iOAT.	**p. 21**
Eligibility	Recommended considerations for eligibility in concert with clinical judgment and precautions	**p. 21**
Medication selection	Both hydromorphone and diacetylmorphine are reasonable choices, based on availability, patient choice, and prescriber judgment	**p. 30**
Titration process	The titration protocol should be followed.	**p. 34, Appendix 7 (p. 77)**
Pre-injection assessment	Performed by a qualified health professional or other trained staff member supervised by a health professional to ensure the patient is not intoxicated or in any other contraindicated acute clinical condition	**p. 31, Appendix 5 (p. 71)**
Administration of injectable medications	Generally, up to 3 visits per day are recommended. Individuals should self-administer under supervision of a qualified health professional. Patients may inject intravenously, intramuscularly, or subcutaneously. Intravenous injection is recommended in upper extremities only. Lower extremity injection should be discussed and risks identified for those who cannot find an appropriate site in their upper extremities or who otherwise prefer intravenous injection in their legs or feet. Intramuscular sites should be identified by a qualified health professional and rotated according to established practice standards.	**p. 32**
Post-intake assessment	Performed by a qualified health professional or other trained staff member supervised by a health professional to ensure safety and attend to dose intolerance or other adverse event.	**p. 31, Appendix 5 (p. 73)**
Co-prescription of oral OAT	Consider co-prescription of slow release oral morphine or methadone to prevent withdrawal and cravings between iOAT doses, particularly overnight.	**p. 34**
Missed doses	The short-acting nature of iOAT medications requires adequate supervision for missed doses. Refer to missed doses protocol.	**p. 36**
Ongoing substance use	Ongoing substance use while on iOAT may be an indication to intensify treatment, which may include dose increases, transferring to a more intensive model of care, and/or increasing psychosocial and other supports. See Ongoing Substance Use for substance-specific guidance.	**p. 42**

3.1 GENERAL CONSIDERATIONS

Injectable opioid agonist treatment is generally considered for individuals[d] with severe OUD who inject opioids and have continued to experience significant health and/or social consequences related to their OUD despite past experience or attempts with appropriately dosed oral OAT[e] (per CRISM's National Guideline for the Clinical Management of Opioid Use Disorder), previous attempts at oral OAT without being able to achieve a therapeutic dose, or other circumstances and risks that indicate the patient may benefit from iOAT. It is important that all health care providers maintain thorough documentation of treatment offers, treatment attempts, overdoses, and patient outcomes in order to ensure that individuals are appropriately transitioned through the continuum of treatment and care, and to document the need for iOAT, when appropriate. Rather than specific doses and dates, the context of the person's life should guide clinician judgment and patients should be adequately counselled on treatment options across the spectrum of care.

The following eligibility considerations are based on published primary literature and experience from existing clinical programs. However, these clinical programs were developed prior to the illicit drug supply in many parts of Canada being contaminated with highly potent synthetic opioids such as fentanyl and carfentanil. Given the high risk of fatal and non-fatal overdose for individuals using illicit opioids in markets where the drug supply has been contaminated, eligibility considerations should address the clinical context. The following eligibility considerations were compiled with the clinical determination, based on decades of clinical and research experience with OAT and iOAT, that pharmaceutical grade opioids prescribed under supervision with sterile injection supplies are safer than illicit opioids.

3.2 PATIENT POPULATION AND ELIGIBILITY

3.2.i Eligibility Considerations

As individual situations vary, considerations for eligibility are presented below, 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. Prescribers[f] are advised to use these consider-

d In line with other clinical guidelines, this document primarily refers to recipients of iOAT as patients, however, where appropriate, other terms such as "individuals", "clients", and "service users" are used to reflect the collaborative and non-hierarchical relationship providers and service users should develop. When working with individuals, their preferred terminology should be sought and mirrored.

e For the sake of simplicity, both oral (methadone and slow-release oral morphine) and sublingual (buprenorphine/naloxone, trade name Suboxone) opioid agonist treatments are referred to as oral OAT in this document.

f This term denotes physicians and nurse practitioners authorized to prescribe iOAT.

ations to guide clinical judgment and collaborative decision-making in determining, with the individual, which treatments have the highest likelihood of ensuring the goals of care, which should include survival, reduction in the harms related to drug use, increased quality of life, and any other patient-defined goals based on their context and needs. It should be noted that these eligibility considerations were informed by inclusion and exclusion criteria in randomized trials and modified according to expert consensus.

Minimum Required Criteria

The assessment and confirmation of these minimum criteria for iOAT are required:

- Confirmed and documented history of injection drug use with opioids and severe opioid use disorder (see DSM-5 criteria in Appendix 4); and
- 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; and
- Capacity to consent to the treatment (see Capacity to Consent in this document for those under 18), including the ability to understand:
  - Level of intensity of treatment
  - Alternate treatment options
  - Potential risks and side effects of iOAT
  - Requirements of inclusion in the program.

Additional eligibility considerations for injectable opioid agonist treatment for those who meet the minimum required criteria include:

- Ability to attend clinic or pharmacy or (where offered) receive home nurse visits up to three times daily;[g]

g Some programs may provide more than three doses per day, such as in jurisdictions where high potency (≥50mg/mL) hydromorphone is not covered, to ensure that patients can receive their needed dose, whereas others may only provide twice-daily doses. Clinical experience in British Columbia has shown that many individuals do well on two doses per day.

- Able to self-administer (i.e., inject via intravenous, intramuscular, or subcutaneous route) medication under supervision or willing to learn, or depending on jurisdiction, model of care, and staffing model, willing to receive health care provider or peer injection (see Appendix 6 in this document for more information on health care provider administration of injectable medications);

- Previous experience with therapeutic dose of oral OAT (per CRISM's National Guideline for the Clinical Management of Opioid Use Disorder) while continuing to experience significant health and social consequences related to their OUD and continued regular injection opioid use, previous attempts at oral OAT without being able to achieve a therapeutic dose, or other circumstances and risks that indicate the individual may benefit from iOAT; and

- Significant risk of medical consequences of injection opioid 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 disorders, history of multiple overdoses).

In addition to the above considerations, the iOAT prescriber, with their patient's consent, should consult members of that person's extended care network (e.g., addiction counsellor, outreach worker, supervised consumption site staff, mental health worker) in order to gain a robust understanding of each patient's individual circumstances. For example, an outreach worker may have important information about the health needs of an individual, such as the circumstances of a recent overdose event. 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, patient experience, input from the patient's network of care providers (who may have relevant information, for example, knowledge of overdoses), and clinical judgement. Clinical judgment and patient preference should balance the benefits and risks of iOAT (which include risk of overdose, seizure, and soft tissue infection) as well as the potential patient burden of up to three visits per day. If the patient is currently receiving oral OAT, the iOAT prescriber should consult with the oral OAT prescriber as part of the assessment process. Additionally, a two-prescriber review for iOAT eligibility may be considered where feasible, and is especially recommended in situations where an individual has not previously been trialed at least once on appropriately dosed oral OAT. While the above criteria are not exhaustive, they reflect current best practices in multiple jurisdictions for determining iOAT eligibility.

3.2.ii Precautions and Cautions

Eligibility Precautions

Caution should be exercised when prescribing iOAT in:

- Youth (under 25 years; see Youth in this document) and older adults,[h] in whom oral OAT or other forms of treatment may be more appropriate.
- Pregnant people or people who become pregnant while receiving iOAT (see Pregnancy in this document).
- Individuals with active moderate or severe alcohol use disorder, due to increased overdose risk. Patients should be treated concurrently for both OUD and alcohol use disorder.
- Individuals with active moderate or severe benzodiazepine use disorder and those prescribed benzodiazepines or z-drugs (e.g., zopiclone, zolpidem). While not necessarily an absolute contraindication, given that concurrent use of benzodiazepines and opioids increases the risk of respiratory depression, overdose, and death,[17-19] caution is warranted. Completing a benzodiazepine taper prior to initiation of iOAT is recommended as the preferred approach.[i]
- Individuals with chronic medical conditions such as respiratory, hepatic or renal disease, acute conditions, or a history of recent head injury.
- Individuals with renal failure. There is evidence indicating that the hydromorphone-3-glucoronide metabolite accumulates in renal failure.[21] Hydromorphone should be used carefully in this setting, although hydromorphone has been used in renal failure patients with no adverse effects. Nephrology consultation is recommended in patients with:
  - GFR < 45
  - Urine ACR > 30mg/mmol
  - Acute kidney injury in absence of readily reversible cause.

h Rather than a specific age range for older adults, determinations should be made based on function, frailty, and specific needs (e.g., living independently, needing extra support, or residing in long-term care facilities). Frailty can be assessed using the Clinical Frailty Scale.[16] In addition, forthcoming guidelines on treating opioid use disorder in seniors should be consulted when appropriate.

i In line with a recent report from the FDA in the US encouraging prescribers to provide OAT for people with OUD even in the context of active benzodiazepine use due to the high risk of overdose from untreated or undertreated opioid use disorder,[20] and in the absence of data regarding risks associated with iOAT and benzodiazepine use, concurrent benzodiazepine use disorder is considered a strong precaution but one that may be handled in more intensive models of care and according to clinical judgment. In those cases, a concurrent benzodiazepine taper should be initiated with iOAT treatment.

- The risk of opioid toxicity inherent in using short-acting medication as is prescribed in iOAT should be individually considered in each case.

General Cautions for Treatment

- Long-term opioid use, including both illicit opioid use and opioid agonist treatment, may lead to abnormalities in the endocrine system, mainly affecting the gonadal axis and leading to hypogonadism.[22,23] In line with this, low testosterone levels and erectile dysfunction have been associated with long-term opioid use (including oral OAT) in males[24] and menstrual disturbances in females.[22] Osteoporosis and reduced bone mineral density can also result from hypogonadism. Clinicians should discuss the potential hormonal changes from chronic opioid use before initiating iOAT and should monitor for its impacts as part of routine care.

- Prescribers should carefully consult the pharmacist associated with their iOAT program regarding drug-drug interactions,[j] including psychotropic medications with sedative effects (e.g., gabapentinoids,[25,26] antipsychotics).

- Individuals with coagulation disorders should be preferentially prescribed oral OAT, due to potential increased risk of bleeding or venous clotting following injection.

3.2.iii Hospitalization

Individuals on iOAT may have comorbidities which put them at increased risk for hospitalization, whether for acute or chronic health conditions. Hospitalization, whether for an acute event or longer-term, should not be understood as an absolute contraindication for iOAT eligibility. Injectable opioid agonist treatment inductions (see Medication Induction) can be performed in a hospital setting with adequate hospital policies and procedures in place. When hospital inductions are performed, the patient should be clinically stable and a physician with expertise in iOAT should assess the patient in hospital. Individuals with existing injection-related infection should be considered medically stable prior to iOAT initiation (e.g., not admitted to ICU, already on appropriate antibiotic therapy, stable vital signs, afebrile) and should receive closer supervision and education around sterile injection techniques. In addition, hospital-based inductions must be done in coordination with an outpatient prescriber and/or program who agrees to receive the patient into care following discharge. See Hospitalization and Acute Pain Events in this document for more information on treating patients on iOAT in hospital.

j Prescribers may also consult the Canadian Pharmacists Association's RxTx tool, available as a subscription both online and in a mobile app, or other subscription-based drug interaction tools.

3.2.iv Youth

The research to date on iOAT has not included participants younger than 18 years old (19 in British Columbia). Thus, the research evidence presented here has been extrapolated from studies conducted in adult populations, with the recognition that prescribers may encounter adolescent (aged 12–17 years) and young adult (aged 18–25 years) populations with severe OUD who do meet some or all of the considerations for eligibility for iOAT in their practice. While it is outside the scope of this guideline to make specific recommendations for the treatment of adolescents and young adults, physicians and nurse practitioners 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, youth-oriented programs, and the ministry charged with the protection of children in each province. Treatment decisions for youth (12-25) should be made by or with consultation from health care professionals with experience in treatment of adolescents and young adults with substance use disorders. If administration of pharmacotherapy to this population is beyond scope of practice, expertise, or experience, care providers should refer such patients to a health care professional with experience in treatment of adolescents and young adults with substance use disorders. For additional guidance in treating youth with opioid use disorder, see the BC Centre on Substance Use's Treatment of Opioid Use Disorder for Youth—Guideline Supplement.

Capacity to Consent

As with any treatment, youth under the legal age of majority in Canada do not necessarily need parental consent in order to receive treatment. Capacity to consent for these youth is determined based on the capacity to fully understand the treatment and possible consequences of treatment, except in Quebec, where the age of consent is 14 years and older,[27] and New Brunswick, where the age of consent is 16 unless two medical practitioners are in agreement that the individual is capable of consenting and that the medical procedure in question is in the patient's best interest.[28] A patient under the legal age of majority seeking treatment who is determined able to understand the treatment and give consent should not require parental permission or notification. Informed consent and discussion of rationale for treatment should be documented, and the limits of confidentiality should be discussed (for example, duty to report). For more information on determining capacity to provide consent in those under the age of majority, refer to guidance from the Canadian Medical Protective Association[27] and Royal College of Physicians and Surgeons of Canada.[28]

Youth-Centered Environment and Approach

Several studies have found that youth (adolescents and young adults) experience the adult-oriented environment of most treatment services as a barrier to accessing and continuing treatment.[29-31] It

should be noted, however, that the evidence base is for substance use disorder treatment more generally, and oral OAT where specified, rather than iOAT. Injectable opioid agonist treatment programs serving youth should ensure that they are relevant, engaging, and accessible in order to engage patients in care.[31] While, generally, the elements that improve retention in adults also apply to youth (e.g., staff who are well-trained, clear policies, and low staff turnover),[32] several youth-specific factors have been identified. These include confidentiality of services,[33] inclusion of family members, the opportunity to develop close relationships with staff, use of pharmacological treatments when appropriate, a combination of pharmacological treatments and psychosocial treatment interventions and supports, and ensuring treatment is provided without a pre-determined end date.[29]

Youth receiving opioid agonist treatment in the United States identified several factors that impact youth engagement in treatment, including a reluctance to access treatment in locations populated by older patients who appeared to have more experience with substance use, as well as the relatability of language and environment.[29] Inclusion of peer navigators and peer support may also support a youth-centered approach, for example, by helping youth who may be ambivalent about receiving care from adult professionals who have not experienced OUD feel more comfortable accessing treatment. Peer support staff, with their own lived experience of OUD, can offer hope, model problem-solving skills, and offer an example of the benefits of participating in OUD treatment.[34]

Where feasible, OAT programs for youth may include iOAT provision. Where youth-specific programs are not feasible, considering the age range of clients and staff when referring youth may prove beneficial for patient retention and the success of the treatment. This consideration should be extended to pharmacy services for youth receiving OAT.

3.2.v Pregnancy and People of Child-Bearing Capacity

To date, published evidence on the feasibility and safety of iOAT during pregnancy is limited to two European case reports, both of which attribute positive pregnancy outcomes to the continuation of treatment with diacetylmorphine in the case of women with severe opioid use disorder and multiple comorbidities.[35,36] In view of the paucity of evidence supporting the safety of iOAT for this population, oral treatment options should always be offered before contemplating the initiation or continuation of iOAT. For transition from iOAT to oral OAT, methadone or slow-release oral morphine may be preferable to buprenorphine/naloxone as it does not require a period of opioid abstinence prior to induction.

However, the potential harms of initiating iOAT should be weighed against the considerable risk of morbidity and mortality associated with untreated opioid use disorder in the case of individuals with severe opioid use disorder who have been unable to stabilize with other options. Similarly, for individuals who are stable on iOAT prior to pregnancy, the likelihood of relapse to non-medical opioid use and associated harms should be carefully assessed when considering treatment de-intensification. In addition to the published case reports, there have been a small number of cases of successful iOAT

continuation through pregnancy provided by services across Europe (M. Vogel, MD, Written communication, November 22, 2017). Decisions concerning the initiation and continuation of iOAT should be made with caution and in consultation with an addiction specialist. The patient's informed consent should be obtained and documented prior to initiating this treatment.

All patients of childbearing capacity starting iOAT should be offered screening for pregnancy at intake, with contraceptive counselling and prescriptions offered as appropriate, and ongoing sexual health and pregnancy planning provided (as is standard in primary care). This is in consideration of the fact that the majority of pregnancies among individuals with substance use disorders are unplanned.[37] In addition, pregnant individuals with substance use disorders may present for prenatal care relatively late in their term due to various social and personal barriers such as fear of losing custody of their children. Family planning services and treatment should also be offered to patients who are currently pregnant in order to reduce the likelihood of a subsequent unplanned pregnancy as short intervals between pregnancies may disrupt ongoing treatment and amplify potential risks to recovery and long-term health.[37]

3.3 PRESCRIBING INJECTABLE MEDICATIONS

3.3.i Initial Considerations

This document is intended to provide guidance on the clinical practice of iOAT provision. Detailed guidance regarding iOAT practice implementation is outside the scope of this document (see iOAT Operations Guidance); however, there are certain minimum requirements which must be considered and addressed at the outset. These include:

- Determining who may prescribe iOAT in each jurisdiction—this may include both physicians and nurse practitioners and will be determined by the appropriate authorities and regulatory bodies in each jurisdiction. See iOAT Operations Guidance.

- Appropriate prescriber training:
  - Each jurisdiction will have its own expectations for training, as determined by ministries of health, regional health authorities, and/or regulatory colleges.
  - At minimum, previous training and experience with both methadone- and buprenorphine/naloxone-based oral OAT prescribing, completion of iOAT-specific training, and a preceptorship (which could be completed remotely through telehealth) are recommended.
    - The BC Centre on Substance Use provides online training on iOAT prescribing through the Provincial Opioid Addiction Treatment Support Program.

- Clinical supervision with a consultant or team leader

- Appropriate staff training—in addition to training on protocols and procedures including supervision of injections and pre- and post-dose observation, staff should be trained and educated on the following:
  - Goals of the program;
  - Approaches and policies on issues like disruptive behaviour, missed appointments, and the importance of consistency across staff;
  - Strategies to make patients feel welcome and supported;
  - Considerations when working with marginalized populations, including trauma-informed approaches and cultural safety and humility. See Providing Care to Groups at Risk of Marginalizing Experiences in this document;
  - Preventing and mitigating stigma by avoiding and rejecting stigmatizing language, labels, and behaviour;[k] and
  - Training in harm reduction philosophy (see iOAT Operations Guidance), practices, and patient education.

- Support of a local pharmacy for medication procurement

- Capacity to provide methadone and/or SROM along with iOAT

- Colocation of psychosocial services, primary care, other medical care (e.g., hepatitis C treatment, wound care, HIV/AIDS treatment), psychiatric care, or well-developed referral pathways

- Consultation on local regulatory framework for provision of hydromorphone and diacetylmorphine (see iOAT Operations Guidance)

- Patient orientation—goals of iOAT, policies and procedures, as well as patient rights and responsibilities should be included in patient orientation. This may include a checklist discussed between staff and patient, peer orientation, and/or other approaches.

k Toward the Heart has multiple resources on reducing stigma, including training modules and guidance on respectful language.

3.3.ii Medication Selection and Preparation

Both hydromorphone and diacetylmorphine can be considered a reasonable choice, however, selection of medication will be subject to availability of diacetylmorphine (see iOAT Operations Guidance for more information).

The SALOME trial, a non-inferiority trial, found that hydromorphone is non-inferior to diacetylmorphine.[13] However, while diacetylmorphine has significantly more evidence supporting its efficacy in treating OUD, it may pose an increased risk of adverse events (e.g., seizures, oversedation) compared to injectable hydromorphone.[13,38] See Appendix 11 for a table of serious side effects for both medications. For these reasons, either medication is a reasonable choice, based on availability, patient choice, and prescriber judgement. If the individual is not benefitting sufficiently or is experiencing unacceptable side effects, they should be given the option to transition to the other medication. See iOAT Operations Guidance for information on availability of diacetylmorphine.

Preparing and Dispensing Hydromorphone

Hydromorphone may be prepared at point of care for immediate use or in advance if appropriate infrastructure and procedures are in place. Beyond use dating is dependent upon several factors, including equipment and infrastructure. Injectable opioid agonist treatment programs should refer to the National Association of Pharmacy Regulatory Authorities (NAPRA) sterile compounding standards[39] and bylaws of each province's regulatory body for pharmacies. Please see the relevant regulatory body's website for more information on bylaws. Health authorities should be involved in providing the service or contracting for pharmacy services within their area. The decision of which format is to be utilized will vary based on the number of individuals 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.

Dispensing and Preparing Diacetylmorphine

Currently, diacetylmorphine is available in 100mL (100mg/mL) vials. In the future, as access to diacetylmorphine expands, and if a Canadian supplier is secured, diacetylmorphine may be prepared at point of care for immediate use or in advance if appropriate infrastructure and procedures are in place. Beyond use dating is dependent upon several factors, including equipment and infrastructure. Injectable opioid agonist treatment programs should refer to the National Association of Pharmacy Regulatory Authorities (NAPRA) sterile compounding standards[39] and bylaws of each province's regulatory body for pharmacies. Please see the relevant regulatory body's website for more information

on bylaws. Health authorities should be involved in providing this medication 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 while this document will be updated regularly, the CRISM website will provide the most up-to-date information.

3.3.iii Medication Provision

Supervision of Injections

Service users self-administer under supervision of a qualified staff member. Any appropriately trained unregulated health care worker may supervise injection as long as a regulated health professional is also in the room and can attend to any issues that may arise. Training for staff members involves orientation to an existing supervised injection program, along with training on conducting pre- and post-injection assessments, responding to dose intolerances, and aftercare.

Supervision of self-administered injection involves completing a pre-injection assessment, direct observation of the injection and disposal of equipment, and a post-injection assessment (see following section for more information on pre- and post-injection assessments). Each visit, including pre-injection assessment, administration of medication, and post-injection assessment, takes between 30 and 45 minutes.

Pre- and Post-Injection Assessment

The purpose of the pre-injection assessment, completed by a qualified health professional or other trained staff if supervised by a health professional (physician, nurse practitioner, 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 iOAT. 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 service users. Appropriate actions in response to these cautions may include holding the dose, reducing the dose, and/or delaying the dose. Prior to iOAT initiation, pre- and post-dose injection assessment procedures should be discussed with the service user and agreed upon as a requirement of the program.

In line with appropriate local regulatory body and nursing standards, any qualified health professional or other trained staff supervised by a health professional can conduct the post-injection assessments; however, any doubts or uncertainties must be reported to a regulated health professional (e.g., physician, nurse practitioner, nurse, or pharmacist) who will complete the post-injection assessment. Patients can leave the premises when they are deemed fit to do so after the minimum 15-minute

observation period post-dose.[l] 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, or slurring. The post-injection observation period may be an ideal time to engage service users in psychosocial services and other medical care, although some individuals may not wish to engage after receiving their dose.

Clinical experience shows that some individuals experience a histaminergic reaction (e.g. swelling, itching) after injecting hydromorphone or diacetylmorphine; this can be managed through dose adjustments and/or provision of oral diphenhydramine or other antihistamines.

The pre- and post-injection assessment protocols can be found in Appendix 5.

Administration of Injectable Medications

It is recommended that patients have access to the iOAT program up to three times per day, however, some programs may provide additional doses per day when feasible and required.[m] Patients self-administer their prepared dose under the supervision of a qualified health professional. Patients may inject intravenously, intramuscularly, or subcutaneously. For safety reasons and to promote sustainable injection processes, it is recommended that intravenous injection be encouraged only in the upper extremities (hands or arms, no jugular or femoral vein use permitted), while intramuscular injections can be allowed in deltoid, ventrogluteal, or dorsogluteal muscles. However, for individuals who cannot find appropriate sites in their upper extremities or who otherwise prefer intravenous injection in their legs, the risks of intravenous injection should be discussed and an informed decision may be made to inject in legs or feet. Subcutaneous injection or short-term transition to oral OAT is also an option for those patients who need to give their veins a rest to heal venous damage.

More guidance on operational considerations is covered in iOAT Operations Guidance, however, each program must ensure the necessary supplies for safe injection are available, including tourniquets, Steri-Wipes, and needles of various gauges. Patients should also receive education on safer injection practices. Vancouver Coastal Health, CATIE, and Here to Help all have useful patient-facing materials on safer injection.

Injection sites should be identified in consultation with a physician, nurse practitioner, Registered Nurse, Registered Psychiatric Nurse, Registered Practical Nurse, or pharmacist (in jurisdictions where pharmacists are permitted to administer medications intramuscularly) and rotated, with the total volume of medication for injection taken into consideration for the most appropriate site, according to

l Each program should create a policy on post-dose observation periods, depending on the context and patient population, which prioritizes patient safety.

m See footnote g, p. 22.

established practice standards (i.e., a large volume should be injected into a large muscle). When clinically indicated and feasible given the particular model of care and jurisdiction (see iOAT Operations Guidance), a physician, nurse practitioner, Registered Nurse, Registered Psychiatric Nurse, Licensed or Registered Practical Nurse, or pharmacist (hereafter referred to as health care provider) can administer the medication intramuscularly or subcutaneously. Nurses with phlebotomy or IV insertion certification may be able to provide IV injection when requested by the patient and determined appropriate. See Appendix 6 for more information on health care provider administration of injectable medication.

It should be noted that route of administration may impact tolerance, and patients should be observed more closely when they switch route of administration (e.g., switching from IM to IV). Some clients may choose to inject some of their dose intravenously and then inject the rest intramuscularly. In these cases, the needle tip should be changed to accommodate each route of administration.

3.3.iv Medication Induction

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 or diacetylmorphine for individuals 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 7.

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

Hydromorphone

Maximum hydromorphone dosages are based on a 2:1 potency ratio of hydromorphone to diacetylmorphine, which was observed in the SALOME study and is supported by clinical experience at Providence Health Care's Crosstown Clinic.[40] Maximum recommended daily doses of hydromorphone can be found in Table 1 below, however, clinical experience in British Columbia shows that there may be clinical exceptions for those who continue to experience cravings and/or withdrawal symptoms. These exceptions should be made according to clinical judgment, with the reason for the exception documented.

Table 1—Maximum Recommended Daily Doses

Medication	Hydromorphone	Diacetylmorphine
Maximum Number of Doses Per Day[n]	3	3
Maximum Daily Dose	500mg	1000mg
Maximum Per Dose	200mg	400mg

Diacetylmorphine

Maximum diacetylmorphine dosages are based on the Swiss clinical studies and were adopted by all of the other settings.[40] Maximum recommended daily doses of diacetylmorphine can be found in Table 1 above, however, clinical experience in British Columbia shows that there may be clinical exceptions for those who continue to experience cravings and/or withdrawal symptoms. These exceptions should be made according to clinical judgment, with the reason for the exception documented.

Titration Process

The initial adjustment of the medication dose should be done over a two- to five-day titration period. A three-day titration period has been shown to be safe,[41] however, clinical practice may vary due to specific patient needs and operational considerations. At any time during the titration period, prescribers 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 individual in order to achieve a safe and effective dose for each person. 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 or nurse practitioner. Patients, in consultation with and under the guidance of their prescriber, can adjust the dose and frequency of daily injection sessions (up to three). Such adjustments can be considered after a visit between the prescriber and the patient, review of 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. A recommended titration process can be found in Appendix 7.

Co-Prescribed Oral Opioid Agonist Treatments

Oral OAT is frequently co-prescribed with iOAT in order to prevent withdrawal and cravings between iOAT doses, particularly overnight during the longest between-dose period, as the injectable medications are relatively short-acting. In this way, co-prescription of oral OAT helps provide greater clinical

n See footnote g, p. 22.

stability. Another potential benefit of co-prescription of oral OAT may be the facilitation of transitions to oral OAT alone. Clinical trials have included co-prescribed methadone, however, SROM may also be considered.[o] Buprenorphine/naloxone is not an appropriate co-prescription; due to its high affinity for the opioid receptor, it preferentially binds to the receptor and displaces other opioids if they are present, which can cause precipitated withdrawal.

Dosing Recommendations

Induction of co-prescribed methadone should follow the process outlined in CRISM's National Guideline for the Clinical Management of Opioid Use Disorder. Guidance on induction of SROM can be found in the BCCSU's A Guideline for the Clinical Management of Opioid Use Disorder. Oral OAT may be started in advance if practical matters require waiting to start iOAT, at the same time as iOAT induction, or after a patient has been titrated onto iOAT.

Co-prescribed oral OAT doses can be given at any time of day. However, it is recommended that SROM be given at a similar time each day to avoid withdrawal, as the preparation is slow-release over 24 hours only, so the effect will not extend beyond 24 hours. Generally, supplemental oral OAT doses should be witnessed, however, prescribers may follow CRISM's National Guideline for the Clinical Management of Opioid Use Disorder's guidance on take-home dosing or provincial standards, when appropriate.

Because of prior experiences receiving only oral OAT with insufficient reduction of cravings and withdrawal symptoms, some individuals may prefer to try iOAT with no co-prescribed oral OAT, on the assumption that oral OAT does not benefit them. Some patients will find a sufficient reduction in cravings and withdrawal symptoms from iOAT alone. For those who are continuing to experience cravings, withdrawal symptoms, or other negative symptoms like disrupted sleep, consider recommending co-prescription of oral OAT to aid their sleep and help provide a baseline level of physical comfort and well-being.

Stable Range of Co-Prescribed Oral Opioid Agonist Treatments

Similar to iOAT doses, co-prescribed oral OAT doses must be determined individually for each patient and will depend, in part, on the patient's goals and circumstances. Doses should be titrated to a dose where there are no withdrawal symptoms between iOAT doses, but may be titrated further in accordance with CRISM's National Guideline for the Clinical Management of Opioid Use Disorder or provincial standards.

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o See Appendix 10 for more information on SROM and iOAT including co-prescription and transition from iOAT to SROM. See CRISM's National Guideline for the Clinical Management of Opioid Use Disorder for a review of evidence supporting the use of slow-release oral morphine more broadly for opioid use disorder.

3.4 MEDICATION STABILIZATION

3.4.i Stable Dose Ranges

Stable doses must be determined individually for each patient and will depend, in part, on the patient's goals and circumstances. A therapeutic dose range has not been established with iOAT, and it is not possible to predict the dose an individual will need based on their history of illicit drug use or previous OAT dosing. Doses should be titrated to a dose where there are no withdrawal symptoms between iOAT doses. While stable doses must be individually determined, mean daily doses from randomized controlled trials on iOAT may be instructive (diacetylmorphine: 443mg;[11] hydromorphone: 244mg[11,13]).

Some patients may wish to further adjust their dose as they achieve psychosocial stabilization and integrate new activities into their lives, for example, once they start working or re-connect with family. In addition to overall wellbeing and a lack of cravings, sleep quality and duration may also indicate when the right dose for a patient has been reached.

For patients wishing to increase their dose, it is recommended that each dose be increased by 10mg (to a maximum of 30mg per day) for hydromorphone and 20mg (to a maximum of 60mg per day) for diacetylmorphine, as long as each dose increase is well tolerated, until their symptoms resolve and they are comfortable, or they reach the recommended dose maximums (200mg/dose and 500mg/day for hydromorphone; 400mg/dose and 1000mg/day for diacetylmorphine).

Table 2: Recommended Dose Increase Protocol

	Hydromorphone	Diacetylmorphine
Dose 1	10mg	20mg
Dose 2	10mg	20mg
Dose 3	10mg	20mg
Maximum increase per day	30mg	60mg

3.4.ii Missed Doses

All iOAT programs should have a missed dose protocol in place which lowers the dose immediately and requires re-titration. When considering the most appropriate missed dose schedule, clinicians should consider opioid tolerance and prioritize safety, with more conservative re-titration approaches used when doses have been missed and tolerance is expected to have been lowered (for example, a patient who has been in a custodial setting without continued illicit opioid use or access to oral OAT). The following missed dose protocol is based on expert consensus and may be modified based on clinical judgment and considerations about safety and tolerance.

- If a new, not-yet stabilized patient misses 3 consecutive doses or 1 day (whichever is first), they should restart the titration process following the titration protocol in Appendix 7.

- If a stabilized patient misses 6 consecutive doses or 2 days (whichever is first), their reason for missing doses should be discussed, their best estimate of the amount and frequency of illicit opioid use should be recorded and, according to clinical judgment, they may receive their usual or a reduced dose provided they meet the pre-dose assessment requirements. See Appendix 8 for an example dose reduction protocol.

- If a stabilized patient misses 9 consecutive doses or 3 days (whichever is first), their reason for missed doses should be discussed, and they should be re-titrated entirely following the titration protocol in Appendix 7.

Unlike the long-acting oral OAT formulations, iOAT medications are short-acting. As such, toxicity effects are more likely to emerge shortly after dose administration, allowing them to be quickly identified within the post-dose observation period in a clinical setting. This may allow for necessary dose adjustments to be made prior to each subsequent dose during the re-titration period to ensure tolerability.

If a client misses a dose or a day, a staff member should follow up with them to ensure their safety and support them in continuing treatment and address any barriers that are interfering with their adherence to treatment. If the client chooses to reduce the frequency with which they receive doses, it should be documented in their chart. In the event that a dose is held due to intoxication found in the pre-dose assessment, it should be considered a missed dose.

The missed dose protocol should be discussed with the patient prior to initiation and agreed to as a requirement of the program.

3.5 CONTINUING CARE

As with any chronic condition, individuals on iOAT should receive comprehensive and continuing care. This should include ongoing review and assessment of adequacy of dosage, side effects, drug-drug interactions, patient goals, physical and mental health, and psychosocial domains including housing, relationships, and finances. Both daily program visits and prescriber appointments can be used for building therapeutic relationships, providing education about harm reduction and safe injection practices, offering supports and referrals to appropriate services, and promoting health and healthy behaviours.

Urine drug testing (UDT) can be used to help guide patient care, to ensure patients are aware of which

substances they are ingesting if using illicit substances, and to start a conversation on harm reduction and safety. Unlike with oral OAT, where regular and random UDT are considered standard of care, regular and mandatory call-back UDT are not considered standard care for iOAT, due to both the low risk of diversion and the high frequency of contact with care providers. See Appendix 12 for more information on UDT.

3.6 TREATMENT TRANSITIONS

This document recommends that iOAT should be provided as an open-ended treatment, given two post-randomized controlled trial observational studies that have found a loss of treatment benefit when prescription diacetylmorphine treatment was discontinued at a predetermined end date (see Appendix 3).[42,43] This document also recommends the use of a stepped and integrated continuum of care model for treatment of OUD, 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 OAT) when patients achieve successful outcomes and wish to transition to lower intensity treatments. It is further recommended that iOAT prescribers support appropriate movement along the continuum of care for patients by being comfortable with prescribing both iOAT and all forms of OAT and 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 individuals 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 program (see Models of Care in iOAT Operations Guidance). Any decisions to de-intensify care from iOAT to oral OAT should be made between patient (and their family, if included in their care), iOAT prescriber, and any other relevant health care providers. This decision should be made with the understanding that treatment modalities across the continuum of care for OUD 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 have their treatment discontinued without consent. If, for example, a patient's prescriber 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.

As with intensification of treatment, 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 immediately reinitiate iOAT. Patients should have the opportunity to trial transitioning to oral OAT and to transition from iOAT to oral OAT and back as many times as necessary in order to maintain their safety and meet their needs and goals.

More information on strategies for de-intensifying treatment can be found in Appendix 10.

3.6.i 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 a daily supplemental dose of oral methadone or SROM, it is critical to establish a conversion factor for switching between methadone or SROM and hydromorphone or diacetylmorphine.

The opioid bioavailability of the individual pharmaceutical agents must be considered when converting dosages. A 100% bioavailability of injectable medication 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 9.

3.6.ii Hospitalization and Acute Pain Events

Individuals on iOAT may have comorbidities which put them at increased risk for hospitalization, whether for acute or chronic physical or mental health conditions. For example, in the North American Opiate Medication Initiative (NAOMI) trial, 53.4% of participants had a chronic medical problem, 62.9% were hepatitis C positive, and 9.6% were HIV positive.[14] For this reason, planning for management of hospitalization and/or acute pain events must be included when initiating community-based treatment.

The following components are recommended in order to support continuity of care:

- Protocol in place for acute care prescribers and addiction medicine consult services to contact the community prescriber;
- Protocol in place for the community prescriber to contact the in-hospital most responsible provider (MRP) to inform them that the patient is on iOAT and, thus, will have a high opioid tolerance;[p]

p Provincial electronic medical records or prescription monitoring programs are ideal, however, in jurisdictions lacking these systems, programs should provide patients with documents (for example, a wallet card) that can be given to acute care providers.

- Protocol in place for community prescriber to contact addiction medicine consult team (AMCT) in hospitals where these services exist. In the absence of these services, the community provider should be consulted to support in-patient care.

- Protocol in place for the hospital team providing care to access date and size of last dose received by patient (for example, uploaded to provincial electronic health record or prescription monitoring program, where possible); and

- Contact information for all iOAT programs, including ability to contact program outside of program hours. Program contact information, including on-call phone number should be included in provincial electronic health record or prescription monitoring program, where possible.

Patients experiencing acute pain events will likely require non-opioid analgesics as well as additional opioids to manage acute pain. Like with oral OAT, the baseline opioid dose will not address acute pain; patients will require higher and more frequent opioid dosing if they have an acute pain event. In addition, when continued in hospital, the iOAT dose may need to be adjusted due to the medications being prescribed for management of acute pain.

In hospital settings where appropriate protocols and procedures are in place, iOAT may be continued (with self-administration or nurse-provided IM or subcutaneous doses). Expert consultation is important for these patients, as doses may need to increase (e.g. acute pain) or decrease (e.g., acute illness leading to an inability to tolerate regular outpatient dose). In hospital settings where iOAT is not feasible or available, alternative oral opioids (for example, oral hydromorphone or SROM) should be provided, with expert consultation to ensure adequate dose and tolerability is instituted.

3.6.iii Considerations for Transitioning Off of iOAT

Once they have reached stability, some individuals may request to transition to an alternative treatment. In other situations, the care team may identify one or more of the following signs that transitioning to oral OAT 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);

- After an adequate trial of iOAT, patients not deriving benefit from treatment (e.g., escalating substance use—including non-opioid substances, repeated episodes of toxicity despite dose adjustments, no reduction in illicit opioid use or related harms);

- Any situation that jeopardizes staff or other patient safety or security and cannot be resolved through other means;

- Cognitive and/or physical health decline resulting in inability to consent to treatment or self-administer medication; 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).

Whenever possible, the decision to transition off of iOAT should be made collaboratively with the patient, with an understanding that the benefits of iOAT may vary between patients and should be based, in part, on patient goals. Examples of benefits include reduced illicit substance use, increased stability, fewer overdoses, less money spent on drugs, and less criminal involvement. 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, which, for some individuals, may include an opioid-free life. Treatment decisions should be made collaboratively and be guided by patient goals, needs, and safety.

3.6.iv Short-term Transition to Oral Treatment for Travel

If individuals receiving iOAT need to travel, they may receive prescriptions for methadone or SROM. 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.[44] For longer absences, daily witnessed ingestion of SROM at a community pharmacy is recommended. Conversely, a slow transition (over 7 to 14 days) to methadone is possible. If the pharmacy is located outside of the patient's province of residence, the prescriber should call the pharmacy to ensure daily witnessed ingestion of SROM or methadone is possible. **Note:** Prescriptions filled outside of the province of residence may not be reimbursed by the patient's provincial drug plan.

For conversions to oral OAT for travel, because of the potential variability in bioequivalency when switching opioids, standard opioid conversions should be used in concert with clinical judgment. All SROM doses should be witnessed ingestion at the dispensing pharmacy. Any missed doses should be reported to the prescriber. See Appendix 9 for more details on conversion.

3.6.v Transition to Oral Treatment Due to Incarceration

Incarceration should not result in inadequate treatment for OUD, and best efforts should be made to provide the best standard of care for OUD regardless of setting. However, at this point in time, iOAT is not provided to individuals in correctional facilities in Canada. It should be noted, however, that there are two prison-based iOAT programs currently in operation in Switzerland.[45] In addition, a 2018 case study reported on the successful integration of iOAT into a drug court treatment program in Vancouver, BC, with positive health and social outcomes reported for the individual.[46]

Patients who have been convicted of a crime and face a period of incarceration must be transitioned to a suitable oral OAT option prior to, or as quickly as possible following, their entry into the correctional system. Detailed recommendations for managing this transition can be found in Appendix 10 of this document.

When an individual receiving iOAT enters a correctional facility, the treatment plan should include the following components:

- Protocol in place for MRP in correctional facility to contact the community prescriber;
- Protocol in place for community prescriber to contact MRP in correctional facility to inform them that patient is on iOAT and, thus, will have a high opioid tolerance;[q]
- Protocol in place for community prescriber to communicate and make recommendations for management should a patient be subjected to a custodial environment while on iOAT;
- Protocol in place for the care team in the correctional setting providing care to access date and size of last dose received by patient (for example, uploaded to provincial electronic health record or prescription monitoring program, where possible); and
- Contact information for all iOAT programs, including ability to contact program outside of program hours. Program contact information, including on-call phone number should be included in provincial electronic health record or prescription monitoring program, where possible.

3.6.vi Continuity of Care

Regardless of which decisions are made regarding transition from iOAT to oral OAT, individuals should have continued access to the ancillary services offered as part of the iOAT program (for example, social workers, housing workers, psychosocial supports) to ensure that continuity is maintained and patients continue to receive a high quality of care.

3.7 ONGOING SUBSTANCE USE

Ongoing substance use while on iOAT may be an indication to intensify treatment, which may include dose increases, transferring to a more intensive model of care, or increasing psychosocial and other

q Provincial electronic medical records or prescription monitoring programs are ideal, however, in jurisdictions lacking these systems, programs should provide patients with documents (for example, a wallet card) that can be given to corrections staff.

supports. If a patient is found to be intoxicated during the pre-assessment, their dose should be postponed or withheld to ensure safety (see Appendix 5). Repeated findings of intoxication in the pre-assessment should be discussed with the patient and should be addressed in a substance-specific manner as outlined below. As described in Harm Reduction-Oriented Care, patients should be advised of the risk of overdose due to contamination of the illicit drug supply with fentanyl and other highly potent synthetic opioids (including non-opioid substances such as benzodiazepines and stimulants), receive education and, where possible, access to a variety of harm reduction strategies, including take-home naloxone, drug-checking facilities, and fentanyl test strips. It should be noted, however, that drug-checking and fentanyl test strips are not well validated and are not available in all jurisdictions.

3.7.i Non-prescribed Opioids

Continued use of illicit (non-prescribed) opioids, ascertained by self-report or urine drug test (see Urine Drug Testing in this document), while on iOAT should be considered an indication to discuss intensification of treatment. Ongoing use at the same intensity as pre-iOAT should be understood as an indication to intensify treatment, however, illicit opioid use in and of itself should not be considered an absolute indication. Some individuals' goals may not include absolute cessation of illicit opioid use. In those cases, harm reduction and overdose prevention should be discussed and reinforced. In situations where intensification of treatment is indicated, clinical judgment should be used in determining what intensification is appropriate. Intensification of treatment may include adding a daily dose of oral OAT (i.e., SROM or methadone), increasing an existing evening dose of oral OAT, increasing the iOAT dose, 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 illicit opioids at the same intensity despite intensification of treatment, clinical judgment should be used to determine appropriate follow up. Reduction from daily illicit injection opioid use may be considered a significant treatment benefit in many cases, however, if the patient is continuing to use illicit opioids or continuing to inject other substances and receiving no benefits from iOAT after intensification and optimization of treatment, treatment cessation may be considered. When considering transition to another treatment approach such as oral OAT, continuity of ancillary services (e.g., mental health care, trauma therapy, primary care) should be ensured. Treatment decisions should be made with the recognition that connection to health care and community are important outcomes of treatment engagement and access to services, and that patients may experience significant benefits from engagement in care, including maintaining housing, connection with family and friends, and decreased crime.

3.7.ii Stimulants

If patients are using stimulants (e.g., cocaine or methamphetamine) while receiving iOAT, the risks and benefits of iOAT should be evaluated to ensure that the person is benefiting from the treatment. Injectable opioid agonist treatment is not a treatment for stimulant use disorder and withholding of doses should be based on patient safety, not used to penalize stimulant use. 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.[47] Preliminary evidence from a single-centre RCT in a European HAT program suggests sustained-release dexamphetamine may be effective for concurrent treatment-refractory cocaine use in iOAT patients, however, more research is needed.[48]

3.7.iii Sedatives (Alcohol and Benzodiazepines)

Ongoing sedative use may indicate a need to intensify treatment. However, due to the additive effect on respiratory depression of both benzodiazepines and alcohol, patients using alcohol and/or benzodiazepines may require a more intensive model of care to ensure adequate management of the co-occurring substance use and patient safety (see iOAT Operations Guidance). Clinical judgment should be used to determine which interventions are appropriate for each patient.

Alcohol

Individuals who present for their iOAT dose intoxicated on alcohol should have their dose withheld due to the increased risk for respiratory depression and overdose. These individuals should be screened for alcohol use disorder and brief intervention should be performed. Clinician-delivered brief intervention, including motivational interviewing, has been shown to reduce alcohol consumption in individuals receiving OAT to treat OUD who had problematic alcohol use but did not meet diagnostic criteria for concurrent alcohol use disorder, however, this was specifically in individuals receiving methadone-based OAT.[49-51]

Due to the high risk of respiratory depression, patients who continue to present for their iOAT dose intoxicated on alcohol should be started on a medication for relapse prevention and agree to ongoing breathalyzer testing before each dose, with doses postponed or withheld if the patient's blood alcohol level exceeds 0.05%. Acamprosate has an established evidence base for safety and efficacy for the treatment of alcohol use disorder.[52-56] For individuals receiving iOAT, acamprosate should be considered along with evidence-based psychosocial treatment interventions and supports for treating concurrent alcohol use disorder,[52,53] and may be dispensed on site. In jurisdictions where acamprosate is not covered by provincial drug plans, an addiction medicine expert should be consulted to discuss other medication options (e.g., topiramate, gabapentin, disulfiram). Due to its effects on opioid

receptors, oral naltrexone cannot be used to treat alcohol use disorder in patients who are on opioid agonist treatment.

Although gabapentin has a growing evidence base supporting its use for withdrawal management[57-60] and preliminary evidence supporting its use in relapse prevention for alcohol use disorder,[61-63] there are specific concerns for individuals with opioid use disorder. This includes the possibility of high doses of gabapentin being combined with opioids to potentiate euphoric effects and the additive effects on respiratory suppression, which can increase risk of overdose.[25] A 2017 Canadian study found that concomitant use of opioid medications and gabapentin increased the risk of fatal overdose by 49%, with moderate and high daily doses increasing fatal opioid overdose risk by 60% compared to those with no concomitant gabapentin use.[26]

Benzodiazepines

Given the known severe risks associated with concomitant use of opioids and benzodiazepines,[17-19] patients with OUD who were using benzodiazepines and illicit (non-medical and/or illegal) opioids concurrently should, ideally, have completed a benzodiazepine taper prior to iOAT initiation. Management of concurrent benzodiazepine use will depend on clinical judgment and model of care, with patient safety prioritized. Prescribers are encouraged to engage a second opinion as needed. Patients who begin using benzodiazepines while receiving iOAT should have the risks of concurrent use discussed with them and initiate a benzodiazepine taper. An increase in treatment intensity, including a more intensive model of care, or increasing evidence-based psychosocial treatment interventions and supports may be required.

3.7.iv Tobacco

Mortality in smokers is almost three times higher than in non-smokers,[64] and is causally linked to significant morbidity including pulmonary disease, coronary heart disease, chronic obstructive pulmonary disease, diabetes mellitus, and multiple cancers including lung, esophageal, and stomach.[65] A 2018 population-based study found that 39% of deaths in individuals with opioid use disorder were due to smoking-related conditions.[66]

Disproportionately high rates of tobacco use have been found in individuals receiving treatment for opioid use disorder compared to general population prevalence rates.[67-70] Looking specifically at individuals receiving iOAT, 94% of participants in the SALOME trial reported tobacco smoking at baseline, with a similar percentage reporting smoking at 6 months.[71]

Although tobacco use disorder is commonly undertreated in addictions treatment,[72] a 2016 Cochrane systematic review found a consistent association between tobacco cessation interventions—both pharmacotherapy and counselling combined with pharmacotherapy—and tobacco abstinence in

individuals in treatment and recovery for substance use disorders, with no evidence showing an effect on abstinence from alcohol and other drugs.[73] Despite common assumptions to the contrary, 44-80% of individuals receiving substance use disorder treatment are interested in tobacco cessation.[74]

Evidence-based treatments for tobacco use disorder, including nicotine replacement therapy, varenicline, and bupropion, should be integrated into iOAT care and delivered onsite when possible.

3.7.v Cannabis

Ongoing cannabis use is not an indication to discontinue iOAT. Patients who are using cannabis recreationally may benefit from a discussion of the recommendations made in the Lower-Risk Cannabis Use Guidelines.[75] Patients who are using medical cannabis should be monitored by their iOAT prescriber to ensure the benefits they receive outweigh the potential harms.

3.8 FAMILY AND SOCIAL CIRCLE INVOLVEMENT IN CARE

This document emphasizes the important role of families—as defined by patients, which may include romantic partners, close friends, and other people of significance who may or may not be legally recognized as family—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. Family members wanting support should be referred to external services and supports, to avoid overlap of service providers, which may impact client trust and create concerns about confidentiality or perceived conflicts of interest.

In the case of youth, parental participation in the treatment of youth should be actively encouraged, if appropriate, and family members should be supported with sufficient information and training. Offering or referring out to group or individual sessions for parents and/or caregivers (e.g., parent guidance sessions) is recommended. In addition to providing emotional support, family members can also function as caregivers and may help ensure that patients regularly attend for their doses and keep appointments.[76]

A family history should be taken, when possible, to identify and treat any mental health or substance use issues requiring treatment in the youth's family. It should also be noted that not all youth have healthy or positive relationships with their family members and decisions to include family members in care should be guided by an understanding of the family dynamic and the patient's wishes.

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 each province's privacy legislations. 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.

3.9 PATIENT-CENTRED CARE

Research suggests that incorporating patient-centred approaches into the clinical management of substance use disorders can improve retention in care, treatment satisfaction, and health outcomes.[77-79] 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.[80] 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, 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, performing 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.

3.9.i Motivational Approach

Motivational interviewing (MI) is a counselling approach that empowers the patient to develop motivation to change, and creates a therapeutic alliance that is predominantly a partnership, rather than an expert/patient dynamic.[81] Motivational interviewing techniques have been adapted for use in primary care settings to support behavioural change and improve self-management for a range of health conditions including HIV/AIDS, diabetes, cardiovascular disease, and substance use disorders.[82-84] Motivational interviewing-based counselling does not require professional specialization and can be delivered by primary care physicians, nurse practitioners, nurses, pharmacists, and other

health professionals who have completed education and training in its delivery.[85] In practice, clinicians engage patients in guided discussion about health behaviours while adhering to the general principles of MI, which are to: 1) express empathy, 2) support self-efficacy, 3) avoid arguing or power struggles, 4) roll with resistance, and 5) develop understanding of discrepancy.[86] The intended outcome is to bring awareness to any discrepancies between current behaviours and future goals.

A 2011 systematic review of MI for treatment of substance use disorders (59 RCTs, n=13,342) found that MI significantly reduced substance use in comparison to no treatment.[85] Further, review results indicated that MI was as effective as other active psychosocial modalities (e.g., cognitive behavioural therapy) as well as assessment and feedback in reducing substance use, although overall the effects were modest in scale.[85] The strongest treatment effects were observed immediately post-intervention, with progressively weaker effects observed at each consecutive follow-up, such that no significant effects were observed more than 12 months post intervention.[85] Additional systematic reviews have reported that MI appears to be most effective when delivered in an individual format rather than group settings, and in combination with assessment and feedback.[82]

It should be noted that there is limited evidence supporting MI for OUD specifically[87,88] and a lack of evidence examining MI in the provision of iOAT, however, motivational interviewing is a common general approach to addiction care across substances.

3.9.ii Trauma-informed Care

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,[89] prescribers 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). There are several useful resources for learning about and integrating trauma-informed practice. These include the Canadian Centre on Substance Abuse's The Essentials of Trauma-informed Care, Klinic Community Health Centre's Trauma-informed: The Trauma Toolkit, EQUIP Health Care's Trauma and Violence-Informed Care Workshop, and the Centre of Excellence in Women's Health's Trauma-Informed Practice and the Opioid Crisis.

3.9.iii Providing Care to Groups at Risk of Marginalizing Experiences

The social determinants of health can be understood as "the social and economic factors that influence people's health."[90] They include income, housing, social exclusion, gender, aboriginal status, race, and disability status, among others,[90] which impact health along a social gradient, with those at the lowest socioeconomic levels experiencing the worst health outcomes.[91] Clinicians providing care

to groups at risk of marginalizing experiences in addition to being an injection drug user (including—but not limited to—Indigenous peoples, racialized people, gender and sexual minorities, women, and people living in poverty) should be sensitive to the ways that these social locations are subject to unequal distribution of power, economic opportunity, and resources,[91] and aware of the fact that a person's multiple social locations (e.g., gender, race, and sexuality) interact with and impact each other,[92] and should endeavour to remove barriers to accessing care patients may experience.

Health care providers should be sensitive to the power differentials inherent in the provider-patient relationship and the ways that the social locations of each (including, but not limited to, race, gender, and class) can further those differentials, as well as the likelihood of previous, concurrent, and future negative experiences in the health care system due to discrimination. EQUIP Health Care provides several resources as well as a Health Equity Toolkit to support health care providers to implement equity-oriented care into primary health care practice.

Each patient will have their own needs, which must be addressed, depending on the social location(s) they inhabit. Examples may include a translator for individuals with limited English or French (depending on provider), connection to immigrant and/or refugee services, and/or referral to gender affirming care for transgender individuals. Safety should be prioritized for all patients, including emotional and cultural safety. Patients belonging to groups at risk of marginalizing experiences may also benefit from patient advocacy, for example, to secure housing, apply for disability assistance, or access psychosocial services, and all patients will benefit from health care providers working to prevent and mitigate stigma by avoiding and rejecting stigmatizing language, labels, and behaviour.

Cultural Safety and Humility When Working with Indigenous Peoples

Health care providers hold social and institutional power, which is amplified when non-Indigenous health care providers treat Indigenous patients. Internalized negative attitudes about Indigenous peoples inform patient-provider relationships and can thus impact the quality of care provided and the client health care experience.[93] The provider-patient relationship is also impacted by health care providers' knowledge of Indigenous cultures, health care providers' understandings of Indigenous health disparities without historical and social context, and the history of colonization in Canada.[93] Structural violence, which can be understood as systemic exclusion, disadvantage, and discrimination, shapes the health of Indigenous peoples in Canada and globally.[94]

It is well documented that Indigenous peoples in Canada are at increased risk of premature morbidity and mortality compared to non-Indigenous populations,[95] and multiple factors are believed to shape these social and health inequalities. Factors that impact health inequalities in all populations, such as environment, access to preventive and primary healthcare, and social determinants of health are believed to have a role, as do factors that are unique to the experiences of Indigenous peoples in Canada, including the impacts of colonization, intergenerational trauma, cultural deprivation,

forced assimilation, and systemic racism and discrimination.[96,97] Research that shows that Indigenous peoples are at increased risk of substance-related harms[95,98] should be interpreted within this context. More specifically, it should be understood that Indigenous peoples are not, by definition, "high-risk" populations; rather, factors such as trauma, discrimination, and systemic racism faced by Indigenous peoples have likely created conditions and experiences of marginalization that, in turn, have led to increased use of opioids and other substances in some individuals as a means of coping with historical and cultural trauma exacerbated by stresses such as racism, violence, poverty, and systemic discrimination in their daily lives.[99,100]

Specific approaches and understandings have been identified as necessary to provide culturally competent care to Indigenous peoples,[101] these include:

- Understanding the importance of local history and the lasting and multigenerational impacts of colonization and the residential school system;
- Examining, understanding, and acknowledging how health care providers' own values impact the healthcare environment and healthcare encounters;
- Understanding health as encompassing physical, intellectual, emotional, and spiritual wellbeing;
- Understanding the impacts of disparities in the social determinants of health;
- Respecting local traditions, traditional beliefs, and healing practices;
- Recognizing and respecting differences in communication styles, which may be influenced by power imbalances as well as cultural behaviours;[r]
- Understanding that whole communities may be impacted by what happens to one community member, that the family unit may be a large, extended family, and that hostile healthcare experiences can influence entire communities healthcare seeking attitudes;
- Understanding that cultural healing practices may require that families be involved in the care of clients;
- Approaching patient relationships with respectful curiosity;
- Challenging personal assumptions, being flexible, and being open to changing how things are commonly done; and

r For example, less eye contact, long silences, and not answering direct questions or replying with a story or longer narrative response may be the norm for some Indigenous peoples compared to non-Indigenous populations.

- Recognizing and accommodating the need for a translator for those whose primary language is not English or French.

For an understanding of how the dominant healthcare system is frequently hostile and culturally unsafe for Indigenous peoples, and how health care providers may lack insight into how their approaches, behaviours, and programs create barriers to Indigenous community members, this document strongly recommends that non-Indigenous prescribers and staff undertake cultural safety and humility training to improve their ability to establish positive partnerships with Indigenous clients seeking care for substance use and related harms. Cultural safety can be understood as an outcome in which people feel safe when receiving care in an environment free from racism and discrimination, which results from respectful engagement that seeks to address power imbalances inherent in the healthcare system. Cultural humility is a process undertaken to understand, through self-reflection, personal and systemic biases, and to develop and maintain respectful processes and relationships based on mutual trust; it requires humbly acknowledging oneself as a learner when attempting to understand another person's experience.[s]

There are several health-specific cultural safety training opportunities online, including training programs and webinars. These are generally designed to increase knowledge, enhance self-awareness, and strengthen the skills of those who work both directly and indirectly with Indigenous peoples. These include the National Indigenous Cultural Safety Collaborative Learning Series, the Ontario Indigenous Cultural Safety Program, Nunavut Program's Cultural Competency Modules, the Saskatoon Health Region Cultural Competency & Cultural Safety Tool Kit, the Manitoba Indigenous Cultural Safety Training, the College & Association of Registered Nurses of Alberta's Cultural Safety Webinar, the San'yas Indigenous Cultural Safety Training developed by the Provincial Health Services Authority (PHSA) Aboriginal Health Program in BC, and First Nations Health Authority (FNHA) and BC Patient Safety & Quality Council's Cultural Safety and Cultural Humility Webinar Series. In addition, in-person trainings are available in some jurisdictions.

2SLGBTQ+ Populations

Two-Spirit, lesbian, gay, bisexual, trans, queer, and other gender and sexually diverse individuals (2SLGBTQ+) face unique challenges that should be addressed when providing care to 2SLGBTQ+ patients with substance use disorders. 2SLGBTQ+ individuals report disproportionate rates of substance use,[102-104] and enter treatment with greater severity of substance use problems.[105] Suggested explanations for these disproportionate rates include the stress of being in a minority group, dealing with social prejudice and discrimination, internalized stigma, and lack of cultural competence in the health care system.[105,106] Data on OUD specifically in 2SLGBTQ+ individuals is lacking, however, given the high

s Definitions borrowed and lightly adapted from the First Nation's Health Authority.

rates of substance use in 2SLGBTQ+ individuals, OUD treatment should be culturally sensitive and include an awareness of the issues that 2SLGBTQ+ individuals are likely to face.

Strategies for working with 2SLGBTQ+ individuals include actively communicating that services are available for 2SLGBTQ+ patients, building relationships with organizations serving diverse marginalized communities, and using inclusive language in forms and clinical materials and during appointments.[105] Although substance use disorder treatment for 2SLGBTQ+ individuals is similar to that for other populations, additional factors must be considered, including acknowledging and affirming the patient's feelings about their sexual and gender identities and the impacts of stigma and discrimination in their lives.[107] Other strategies include respecting that identities are fluid and tailoring care accordingly; mirroring the language that your patients use (e.g., to refer to themselves, their relationships, and their bodies); not assuming sexual activity levels or motives for substance use; and being affirmative—recognizing the ways that individuals successfully practice harm reduction in their lives. 2SLGBTQ+ individuals may also have experienced discrimination in the health care system and thus require extra sensitivity from health care providers in order to build trust.[107] Prescribers should make themselves aware of local support groups and resources for 2SLGBTQ+ individuals. Additional information and guidance can be found in the Substance Abuse and Mental Health Services Administration's publication, A Provider's Introduction to Substance Abuse Treatment for Lesbian, Gay, Bisexual, and Transgender Individuals.

A non-judgmental attitude, active demonstration of awareness of and sensitivity toward trans issues, and a reinforcement of confidentiality can help trans people feel safe approaching care providers.[108] Other ways to demonstrate transgender awareness and sensitivity include placing trans inclusive brochures and posters in waiting rooms, asking about gender identity on intake forms (and avoiding conflating gender and sex[t]),[108] and using open-ended questions about sexuality and gender.[107] Additional strategies include being reflexive and acknowledging personal biases; recognizing an individual's intersecting identities (e.g., race, disability, gender, sexuality) and how they may compound and impact patients' experiences of health care; making gender neutral bathrooms available; and respecting that identities and pronouns are fluid and can change. More information on working with trans, Two-Spirit, and gender diverse patients can be found in Trans Care BC's Gender-affirming Care for Trans, Two-Spirit, and Gender Diverse Patients in BC: A Primary Care Toolkit. Additional resources include the Trans Care Program in British Columbia, Rainbow Health Ontario, "Je m'engage"—a guide for Quebec health and social service providers, and the Canadian Professional Association for Transgender Health.

t Sex generally refers to the classification of a person as male, female, or intersex at birth, usually based on the appearance of their external anatomy, whereas gender refers to one's internal, deeply held sense of their gender, which may or may not align with the sex they were assigned at birth. A person's sex should not be assumed to match their gender; for example, that a person will have specific genitalia or reproductive anatomy based on their gender identity.

Two-Spirit[u] is term used by some North American Indigenous societies to describe people with diverse gender identities, gender expressions, gender roles, and sexual orientations. Dual-gendered, or 'Two-Spirited' people have been and are viewed differently in different Indigenous communities. Additional information on Two-Spirit individuals can be found on the Two Spirit Journal website.

3.9.iv Wellness and Self-Defined Progress

One of the goals of treatment across the continuum of care for OUD should be wellness, with an understanding that wellness looks different for each person, with many different possible paths. For some individuals, this may include a concept of recovery, which can be understood as "A process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential,"[109] while others may have other personal definitions of wellness and progress.

Those seeking wellness require understanding, support, and referral to appropriate services to achieve their goals. Injectable opioid agonist treatment care teams are encouraged to incorporate and use language that promotes wellness in their practice. This includes ensuring respect of the patient's autonomy and individuality, emphasizing skills and strengths, and avoiding reinforcement of paternalistic models of care provision.[110] Additionally, and as appropriate, iOAT prescribers and care teams are encouraged to work collaboratively with patients to develop long-term, personalized, strengths-based wellness 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 wellness planning, iOAT providers should consider incorporating peer navigators to support long term, patient-centered treatment goals.

3.9.v Role of peers

The vital importance of peer navigators and peer support should be recognized across the continuum of care for opioid use disorders, including individual peer/patient navigation and advocacy as well as the work of drug user organizations, including the Canadian Association of People Who Use Drugs (CAPUD) and the Vancouver Area Network of Drug Users (VANDU), in advocating for expansion of iOAT and the need for it to be low-barrier, especially in the current context of criminalization creating a toxic drug supply contaminated with fentanyl and other highly potent synthetic opioids.

"Nothing About Us Without Us": Greater, Meaningful Involvement of People Who Use Drugs: A Public Health, Ethical, and Human Rights Imperative identifies several important benefits to peer involvement especially relevant for the provision of iOAT. These include more patient "buy-in" to the

u Term borrowed and lightly adapted from Qmunity's "Queer Terminology from A to Q "

program; the ability for patients' needs to be recognized and addressed; service delivery that meets the needs of patients by being realistic, low-barrier, and useful; and providing a sense of ownership for peers.[111] A qualitative study of a peer-run overdose response program in emergency shelters identified several factors that lead to increased feelings of safety from peer workers compared to non-peer paid staff, including social safety due to shared experiences, an absence of uneven power dynamics, and a perception of being cared for that contrasted with their everyday experiences.[112] Peer workers working at VANDU have identified several significant benefits to their work, including decreased risks associated with sex work, drug dealing, or theft as well as increased social contact, social recognition, structure, collective purpose, and an acknowledgment of their work.[113]

Peer Orientation and Education

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. Some patients starting iOAT have not previously been engaged in care in the health system; these patients may benefit from peer support in navigating the system and advocacy as needed.

Peers should also be included in educational efforts for potential patients and the larger community. Working with peers to create clear messaging about the expectations, benefits, and requirements of iOAT will help ensure that new patients have realistic expectations for the treatment.

3.9.vi Harm Reduction-oriented Care

Broadly defined, harm reduction refers to policies, programs, and practices that aim to reduce the adverse health, social, and economic consequences of licit and illicit substance use.[114] Across Canada, established harm reduction initiatives include needle/syringe distribution programs, overdose prevention with take-home naloxone, and supervised injection or consumption services. Including these harm reduction approaches within the continuum of addiction care provides additional mechanisms for promoting health and safety in diverse patient populations, including individuals who have difficulties achieving abstinence or who relapse to non-medical opioid use. There is substantial evidence that uptake of harm reduction services is associated with significant decreases in substance-related harms, including risky behaviours, HIV and hepatitis C infection, and overdose deaths.[115-122] In addition, research has shown that participation in harm reduction services can promote entry into addiction treatment.[123-126] For these reasons, if a patient is at risk of opioid-related harms, providing information and referrals to harm reduction services is a reasonable and appropriate clinical decision, particularly in the current environment of heightened overdose risk. Beyond specific harm reduction interventions, programs should take a non-punitive approach to treatment that utilizes a strengths-based approach and meets patients where they are.

There are a number of actions clinicians can take to increase awareness of harm reduction services among patients. These include patient education about harm reduction and safer injection practices, including drug-checking services (where available) and take-home fentanyl testing, with a discussion of the limitations of these interventions. In order to provide informed referrals, clinicians should also be aware of harm reduction programs available in the local area and services provided. Additional information on harm reduction principles and available harm reduction services across Canada can be found in the iOAT Operations Guidance.

3.9.vii Naloxone

Where possible, all iOAT patients should receive overdose prevention education and a take-home naloxone kit at the start of injectable opioid agonist treatment and have ongoing and continuous access to harm reduction services and supplies. Families, colleagues, friends, and other loved ones should also be engaged to receive overdose response and prevention education and naloxone training. See Appendix 13 for guidance on responding to dose intolerances.

3.9.viii Mental Health Care

Mental health and substance use disorders frequently co-occur. Twelve-month prevalence rates for adults in the US with a substance use disorder and any concurrent mental health disorder were 43.3% in 2016,[127] while over 50% of individuals with a severe mental illness are estimated to have problematic substance use.[128] Looking specifically at opioid use disorder, an observational study of individuals receiving methadone-based OAT in Ontario found that 78.5% met diagnostic criteria for at least one comorbid psychiatric disorder, with anxiety disorders most common.[129] A 2017 meta-analysis examining the treatment of mood and anxiety disorders in individuals receiving OAT found psychotherapy and tricyclic anti-depressants most effective. Selective serotonin reuptake inhibitors (SSRIs) were not significantly better than placebo.[130]

Patients who present with opioid use disorder should be screened for concurrent mental health disorders, and those who screen positive should receive evidence-based treatment for both. Generally, OUD and any comorbid mental health disorders should be treated concurrently, however, with severe OUD, stabilization—including initiation of iOAT—may be prioritized initially, with concurrent treatment once stability has been achieved.

3.9.ix Referral Pathways

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 services meant to improve quality of life and address social determinants of health. Some programs may co-locate or partner with community organizations which provide psychosocial services, others may offer some services on-site (e.g., counselling, housing workers) and refer out to other community services, and others will utilize referral pathways to ensure service users can access the psychosocial services they need and will benefit from. 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 where appropriate, for example, for women, youth, immigrants and refugees, and Indigenous peoples.

3.9.x Treatment Plan

Prescribers should work collaboratively with patients and their care teams to create and continuously revisit treatment plans based on each patient's goals, health, and circumstances. Treatment plans should use a comprehensive approach that includes assessment and treatment of any mental health or other comorbidities, psychosocial treatment interventions including cognitive behavioural therapy and motivational enhancement therapy, psychosocial supports (e.g., housing, education, and employment support), recovery services, and, when appropriate, family involvement in care; however, the creation of a comprehensive treatment plan should not be considered a pre-requisite to initiating iOAT and may be expanded as patients stabilize and their needs and goals change. Treatment plans should factor in age, gender, substance use history and trajectory, any experiences of violence, exploitation, trauma, and other factors that may support or negatively impact treatment adherence, including romantic partners, gender identity, sexual orientation, and family history.

Patients and care teams may also benefit from filling out a client safety care plan or behaviour agreement. This may include identifying triggers or irritants, calming strategies, and an agreement for how staff will respond if a patient is upset. In addition to building this plan or agreement together, the conversation that accompanies this agreement can represent an important relationship-building opportunity. A sample client safety care plan is available on the CRISM website.

3.9.xi Cost and Coverage

See iOAT Operations Guidance for information on cost and coverage of iOAT.

Appendices

APPENDIX 1: EVIDENCE SUPPORTING INJECTABLE OPIOID AGONIST TREATMENT FOR OPIOID USE DISORDER

Injectable Opioid Agonist Treatment in Other Jurisdictions

The United Kingdom has provided unsupervised prescription injectable diacetylmorphine for the treatment of OUD for over a century.[131] Supervised prescription diacetylmorphine treatment has been available in Switzerland starting with a national clinical study in 1994,[132] 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.[133] More recently, Germany, Denmark, and the Netherlands have also adopted supervised prescription diacetylmorphine treatment for those with severe, treatment-refractory OUD.[134] In these countries, diacetylmorphine is used for <1% to 12% of all patients engaged in treatment for OUD.[134-136] The Comprehensive and Dedicated Injectable Opioid Agonist Treatment Program model has been widely applied in European jurisdictions,[v] wherein patients receive comprehensive addictions care, with the aim of meeting as many of the patients' 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.[134]

Evidence Summary

Two 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 illicit heroin use, criminal activity, and involvement in sex work, as well as improving overall health and social functioning.[11,12] 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 illicit drugs.[11] The authors of the Cochrane review concluded that there is value in co-prescribing diacetylmorphine with flexible doses

v Switzerland, Germany, Denmark, and the Netherlands use this model. The UK's unsupervised take-home model and Spain's limited weekday clinics are exceptions.

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 opioid agonist treatment.[11] 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.[12] 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 illicit heroin use among individuals who received supervised injectable diacetylmorphine compared to those who received oral methadone treatment only.[12] Further supporting the use of iOAT for those who have not benefitted from oral OAT, a 2017 evidence review undertaken and released by Public Health Ontario concluded that the available literature on iOAT demonstrates efficacy for iOAT over methadone in terms of treatment retention, reduction in illicit drug use, and reduction in criminal activities.[137]

Although treatment with diacetylmorphine is a standard of care in a number of countries,[134] it is considered an emerging treatment in Canada and, currently, can only be accessed through Health Canada's Special Access Programme or inclusion in Health Canada's List of Drugs for an Urgent Public Health Need. Due to 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 individuals with long-term, treatment-refractory OUD.[13] After six months of treatment, researchers found that injectable hydromorphone was not inferior[w] to injectable diacetylmorphine for long-term injection street opioid users not currently benefitting from available treatments.[x] Both medications, delivered in identical conditions, have been shown to have positive outcomes such as high retention rates (over 77% ITT; over 92% PP), reduction of street opioid use (from daily to a few days per month) and illegal activities.[13] Thus, in jurisdictions where diacetylmorphine is currently not available, or in patients where it is contraindicated or unsuccessful, hydromorphone provides an effective, licensed alternative.[13]

Treatment Duration

To date, two studies have found 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 (12 months).[42,43] Thus, the authors of the Treatment Assisted by DAM (diacetylmorphine) 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.[42,138]

w This study was a non-inferiority trial, which is a study design 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.

x 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.[13]

Expanded Eligibility

The majority of clinical trials evaluating iOAT have restricted participation to individuals who have previously undergone oral OAT treatment; thus, the evidence base can be understood as being supportive of iOAT 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.[139,140] 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.[139] Clinical practice in British Columbia has also shifted to broader eligibility considerations, which includes past experience with appropriately dosed oral OAT while continuing to experience significant health and social consequences related to their OUD; multiple attempts at oral OAT without being able to achieve a therapeutic dose; or other circumstances and risks that indicate the individual may benefit from iOAT. In addition, some European jurisdictions have expanded their eligibility criteria beyond those who have tried and not benefitted sufficiently from oral OAT.

Safety

Optimizing patient safety has been an important factor in the designation of iOAT as an alternative intervention when oral OAT has not been successful (in jurisdictions where iOAT is available), and in 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 iOAT, the more rapid onset of action and shorter duration to reach peak effects (including respiratory depression) achieved with injection rather than oral ingestion of high-dose, full agonist opioid medications must also be considered. For this reason, and as emphasized throughout this document, iOAT should only be administered in designated clinical settings, with sterile supplies, 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.[12] Each of these incidents was safely managed with appropriate resuscitation measures, which speaks to the necessity of injection being supervised by trained staff.[12] It should be noted that hydromorphone had significantly fewer adverse events and serious adverse events (SAEs) in the SALOME trial,[13] and thus diacetylmorphine

may pose an increased risk of other adverse events (e.g., histamine reactions, seizures, and overdose) compared to injectable hydromorphone[13] and oral methadone.[11,12] The majority of SAEs occur within a few minutes of receiving an injection,[140] therefore, the recommended post-injection supervision period of 15 minutes, which would be required regardless of program type or treatment setting, is 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 from illicit opioid use not in the treatment setting, as demonstrated by a non-statistically significant reduced mortality risk compared to oral methadone alone.[11,12]

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 sterile needle in a clinical 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 illicit drugs. 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.[141] 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.[38] Although difficult to compare and more data is needed, this is compared to 6-12 month prevalence rates of skin and soft tissue infections in people who inject illicit drugs, which range from 6.9% to 37.3%.[142] Additionally, the risk of contracting a blood-borne illness (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 oversedation or 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.[11,12,38] 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 illicit 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.[12]

Cost Effectiveness

Studies in both Europe and Canada have found injectable diacetylmorphine treatment to be more cost-effective than oral methadone treatment, due to significant reductions in criminal activity and the costs associated.[143-145] Similarly, hydromorphone has been found to be more effective and less costly than oral methadone treatment, due to significant reductions in criminal activity and hospitalization and the associated costs.[146] It should be noted that these cost savings rely on the effective negotiation of hydromorphone prices. In addition to cost effectiveness, data from British Columbia shows that individuals receiving injectable hydromorphone and diacetylmorphine gain more quality-adjusted life years (QALYs) than individuals receiving methadone (8.4 [95% CI=7.4 to 9.5]) and (8.3 [95% CI=7.2 to 9.5]) versus (7.4 [95CI=6.5 to 8.3]), respectively.[146]

APPENDIX 2—DEVELOPMENT PROCESS

Content Development

The medical writer and committee co-chairs, on behalf of CRISM, developed this national guideline using a structured literature review approach. Relevant search terms and structured search strategies were used to search PubMed, the Cochrane Library databases, and reference lists (up to August 1, 2019) using a hierarchical approach, whereby meta-analyses and systematic reviews were given the most weight, followed by individual randomized controlled trials (RCTs), quasi-experimental studies, observational studies, and, lastly, expert opinion. The medical writer manually reviewed titles, abstracts, and full text of identified citations, selected evidence for inclusion, and compiled narrative evidence reviews, including cost effectiveness data, for the guideline co-chairs and the guideline review panel. Grey literature searches were also conducted for any other existing iOAT guidelines and international researchers and other experts in the field were engaged to determine whether iOAT guidelines exist anywhere in the world. While some individual clinics have various protocols and manuals, this process determined that the BC Centre on Substance Use's 2017 provincial Guidance Document for Injectable Opioid Agonist Treatment for Opioid Use Disorder is the only clinical guidance document in existence, to date. Any questions or uncertainties in the literature search, evidence review, and synthesis processes were brought to the chairs for clarity and consensus.

Review Process

The National iOAT Clinical Guideline was written by the National iOAT Clinical Guideline Review Committee. Once finalized, the clinical guideline was reviewed by the National iOAT Operational Guidance Review Committee, followed by external review by people with lived experience, experts in the subject matter, and a family member impacted by opioid use disorder.

Composition of Guideline Review Committee

The CRISM National iOAT Steering Committee was assembled to coordinate guideline preparation activities including recruiting the committee, with representation sought from each of the four CRISM nodes (BC, Prairies, Ontario, and Quebec-Atlantic). The Steering Committee included representation from BC, Alberta, Ontario, and Quebec; each member had relevant expertise, including injectable opioid agonist treatment prescribing, research, and service planning. The Steering Committee decided to create two complementary documents: A clinical guideline and an operational guidance document. To that end, the Steering Committee assembled expert committees for each document. Each member of the Steering Committee was invited to nominate relevant experts from their own province and across the country. As committee members accepted the invitation to join, they were encouraged to nominate additional members to ensure a diverse committee representing a range of experience and expertise. Final committee composition was determined by co-chair consensus. The National iOAT Clinical Guideline Review committee was

composed of 30 individuals, including the two co-chairs, which included physicians, nurses and nurse practitioners, pharmacists, people with lived experience, researchers, treatment providers, and front-line staff.

Development of Recommendations

Recommendations were developed and graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool[147-150] through an iterative consensus process. Draft recommendations were developed by the committee co-chairs and medical writer, then revised by the full committee in two consecutive rounds of review, as described below. Following each round of review, the medical writer revised the recommendations, incorporating all feedback received from committee members. Recommendations were agreed upon by committee consensus. External reviewers did not provide input on the three key recommendations. The committee co-chairs then reviewed and approved the final version of recommendations (more detailed explanation of the evidence underlying each recommendation and score is available in Appendix 3).

GRADE Approach and Interpretation of Grading

The GRADE approach[147-150] to rating quality of evidence starts with a simplified categorization of study types (meta-analyses and randomized controlled trials (RCT), quasi-experimental studies, observational studies, and expert opinion), accompanied by initial estimated levels of confidence (high, moderate, low, or very low) in the estimate of a treatment effect. The rating scheme allows for factors that would raise or lower a level of confidence. Factors that would lower confidence in evidence include risk of bias, inconsistency across the RCTs, indirectness, and publication bias; factors that would increase confidence include large effect size and an observed dose–response effect. The final quality ratings are reflective of the confidence in the estimated effect in context of bias and limitations that have been identified, as described below:

- High: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The GRADE approach uses a binary system to classify strength of recommendations as either strong or weak/conditional. For this guideline, “conditional” was used rather than “weak.” It is important to note

that, although quality of evidence is an important factor when classifying strength of recommendations, "strong" or "conditional" in this case does not refer exclusively to the quality of evidence underlying a given recommendation. Except for cost and resource allocation, the recommended GRADE factors to classify strength of recommendations were considered:

- Balance between desirable and undesirable effects: The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a conditional recommendation is warranted.

- Quality of evidence: The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted.

- Values and preferences: The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a conditional recommendation is warranted.

Interpretation of Strength of Recommendations

Examples of how a strong versus conditional recommendation could be interpreted by selected audience or user groups are listed below.

A strong recommendation indicates the following:

- **For patients:** Most people in your situation would want the recommended course of action and only a small proportion would not; you should request discussion with your care provider if the intervention is not offered.

- **For clinicians**: Most patients should receive the recommended course of action. As an example, in this scenario, an algorithm or decision-making tool would not be necessary—the benefits of the recommended course of action would clearly outweigh any advantages of alternative interventions.

- **For health care administrators:** The recommendation can be adopted as a policy in most situations.

A conditional recommendation indicates the following:

- **For patients:** Most people in your situation would want the recommended course of action, but many would not.

- **For clinicians:** You should recognize that different choices will be appropriate for different patients and that you must help each patient to arrive at a management decision consistent with her or his values and preferences. In this scenario, an algorithm or decision-making tool would be advantageous to determine the best course of action.

- **For health care administrators:** Policy-making will require substantial debate and involvement of many stakeholders.

Review of Recommendations

The review process consisted of one round of revisions of the draft guideline recommendations and evidence review by the pan-Canadian review committee. The medical writer and committee co-chairs consolidated guideline revisions as needed to address committee feedback. Differences in opinion or interpretation with regard to the guideline recommendations or the evidence review were resolved through facilitated discussions in a committee teleconference or direct communication. A final decision was reached for all cases without the need for arbitration.

Management of Competing Interests

This guideline was entirely funded through the CIHR-funded CRISM network and without pharmaceutical industry support. Competing interests were assessed using the Guidelines International Network's Principles for Disclosure of Interests and Management of Conflicts in Guidelines.[151] No current or ongoing direct competing interests were disclosed by the 30 members of the clinical sub-committee on screening for participation in the review committee. No individual reported a history of employment (either self or family member); consulting or advising; honoraria or fees for training, speaking, or panel discussions; investment interests; grants-in-aid for research, non-monetary research or program support (e.g., equipment, travel, staff salary, facilities); or intellectual property holdings with industry or any commercial entity that could potentially benefit from guideline recommendations. In terms of indirect sources of potential interest or bias, overall, 21 individuals disclosed special interests in relation to the guideline content. These pertained to specific expertise and/or clinical experience (e.g., addiction medicine clinician, academic addictions expert), involvement with provincial OAT or iOAT programs and committees, or research interests and publications. No individual reported that his/her clinical revenue would be influenced by the guideline recommendations. Upon review by the committee co-chairs, none of the potential direct or indirect conflicts of interest or bias disclosed by committee members were deemed to be of sufficient relevance or weight to warrant the members' exclusion from the committee.

All 30 committee members participated in multiple rounds of review and revision of the draft and granted final approval of the guideline contents and clinical recommendations.

External Review Process

This guideline was reviewed by the National Injectable Opioid Agonist Treatment Operational Guidance Review Committee, which was responsible for the development of its partner document. Following this review, it underwent external review by people with lived experience, experts in the subject matter, and a family member impacted by opioid use disorder.

Update Schedule/Process

In line with AGREE II criteria,[152] every two years a structured literature search from the last date update will be conducted and the National iOAT Clinical Guideline Committee will be reconvened to determine which updates from research evidence and expert consensus should be added.

APPENDIX 3—RECOMMENDATIONS AND EVIDENCE SUMMARIES

The GRADE approach[147-150] rates quality of evidence and strength of recommendation. More information on the GRADE approach is available in Appendix 2. A brief overview of the rating system precedes the recommendations and evidence summaries.

Quality of Evidence

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Strength of Recommendation

	Strong	**Conditional**
For patients	Most people in your situation would want the recommended course of action and only a small proportion would not; you should request discussion with your care provider if the intervention is not offered.	Most people in your situation would want the recommended course of action, but many would not.
For clinicians	Most patients should receive the recommended course of action. As an example, in this scenario, an algorithm or decision-making tool would not be necessary—the benefits of the recommended course of action would clearly outweigh any advantages of alternative interventions.	You should recognize that different choices will be appropriate for different patients and that you must help each patient to arrive at a management decision consistent with her or his values and preferences. In this scenario, an algorithm or decision-making tool would be advantageous to determine the best course of action.
For health care administrators	The recommendation can be adopted as a policy in most situations.	Policy-making will require substantial debate and involvement of many stakeholders.

Recommendation 1	
Injectable opioid agonist treatment should be considered for individuals with severe, treatment-refractory opioid use disorder and ongoing illicit injection opioid use.	
Quality of Evidence: **Moderate**	Strength of Recommendation: **Conditional**

Remarks:

The rapid onset of action and shorter time to reach peak effects (including respiratory depression) that is achieved with injection rather than oral ingestion of high-dose, full agonist opioid medications necessitate that iOAT be administered in 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.

The majority of clinical trials evaluating iOAT have restricted participation to individuals who have previously undergone, but not benefited from, oral OAT treatment; thus, the evidence base is supportive of iOAT 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.[139,140] 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.[139] Clinical practice in British Columbia has also shifted to broader eligibility considerations, which includes past experience with appropriately dosed oral OAT while continuing to experience significant health and social consequences related to their OUD; multiple attempts at oral OAT without being able to achieve a therapeutic dose; or other circumstances and risks that indicate the individual may benefit from iOAT based on clinical judgment.

This treatment should be offered to and discussed with all those patients who may benefit from it.

It was decided that this recommendation should be conditional due to the high intensity of treatment requiring (in most cases) multiple trips to the clinic or pharmacy per day, which may be experienced as overly onerous for some patients; the increased risk of adverse events compared to oral OAT;[11,12] the potential for other treatment approaches being collaboratively decided as the best option by clinician and patient; and the likelihood that policy-making will require substantial debate and involvement of many stakeholders.

To date, there has not been research conducted specifically looking at iOAT provision in youth. Specific considerations for youth (adolescent—aged 12–17 years; and young adult—aged 18–25 years) populations with severe OUD who do meet some or all of the considerations for eligibility for iOAT in their practice are outlined in this clinical guideline.

Evidence Summary:

Two systematic reviews, which included 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 illicit heroin use, criminal activity, and involvement in sex work, as well as improving overall health and social functioning.[11,12] These meta-analyses include a 2011 Cochrane Review which 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 (4 RCTs; n=1388, Relative Risk (RR) 1.44 [95% confidence interval (95% CI) 1.19 to 1.75])[11] and a 2015 systematic review and meta-analysis which found supervised injectable heroin treatment

to be superior to methadone in treating treatment refractory opioid use disorder (4 RCTs; n=1377, RR 1.37 [95% CI 1.03 to 1.83]).[12] Both systematic reviews also reported greater reductions in illicit drug use (both heroin and other illicit substances), however, due to heterogeneity in reporting, these were reported narratively rather than included in the meta-analyses.

In response to restrictions on accessing diacetylmorphine in Canada, the Study to Assess Longer-term Opioid Medication Effectiveness (SALOME) compared diacetylmorphine with injectable hydromorphone in a population of patients (n=202) with long-term, treatment-refractory OUD.[13] Both per protocol (PP) and intention to treat (ITT) analyses found that injectable hydromorphone was not inferior to injectable diacetylmorphine for long-term injection street opioid users not currently benefitting from oral opioid agonist treatment, in terms of retention rates (≥92% PP; ≥ 77% ITT), reduction of any street opioid use (-0.15 [90% CI -2.09 to 1.76] PP; -0.85 [90% CI -2.97 to 1.25] ITT), and illegal activities (-1.06 [95% CI -3.46 to 1.14] PP; -0.98 [95% CI -3.11 to 1.04] ITT). Per protocol analysis also found non-inferiority for reduction in street heroin use (-1.44 [90% CI -3.22 to 0.27]).[13] Thus, in jurisdictions where diacetylmorphine is currently not available, or in patients where it is contraindicated or unsuccessful, hydromorphone provides an effective, licensed alternative.[13]

Recommendation 2	
For patients who are determined to be likely to benefit from injectable opioid agonist treatment, both diacetylmorphine and hydromorphone are acceptable treatment options.	
Quality of Evidence: **Low**	Strength of Recommendation: **Strong**
Remarks: Both hydromorphone and diacetylmorphine are approved for the treatment of opioid use disorder in Canada. However, diacetylmorphine must be applied for through the Special Access Programme for individual patients or added to the List of Drugs for an Urgent Public Health Need for a given jurisdiction. Either medication may be considered a reasonable choice, based on availability, patient choice, and prescriber judgement. If the individual is not benefitting sufficiently or is experiencing unacceptable side effects, they should be given the option to transition to the other medication. The quality of evidence is rated low due to the discrepancy in evidence supporting each medication, with two systematic reviews supporting the use of diacetylmorphine, and only a single study supporting the use of hydromorphone. The recommendation is rated as strong based on expert consensus, significant clinical experience in British Columbia, reduced risk of adverse events for hydromorphone compared to diacetylmorphine, and the lack of regulatory and supply barriers impacting access to hydromorphone.	

Evidence Summary:

As outlined above, two systematic reviews support the recommendation of diacetylmorphine for the treatment of severe opioid use disorder.[11,12] Due to regulatory barriers which limited access to diacetylmorphine in Canada, the SALOME trial compared injectable hydromorphone to injectable diacetylmorphine in a non-inferiority trial and found no evidence indicating that hydromorphone is inferior to

diacetylmorphine.[13, 28] Both per protocol and intention to treat analysis found that injectable hydromorphone was not inferior to injectable diacetylmorphine for long-term injection street opioid users not currently benefitting from oral opioid agonist treatment, in terms of retention rates (≥ 92% PP; ≥ 77% ITT), reduction of any street opioid use (-0.15 [90% CI -2.09 to 1.76] PP; -0.85 [90% CI -2.97 to 1.25] ITT), and illegal activities (-1.06 [95% CI -3.46 to 1.14] PP; -0.98 [95% CI -3.11 to 1.04] ITT). Per protocol analysis also found non-inferiority for reduction in street heroin use (-1.44 [90% CI -3.22 to 0.27]).

While diacetylmorphine has significantly more evidence supporting its efficacy in treating OUD, it may pose an increased risk of adverse events (e.g., seizures, and overdose) compared to injectable hydromorphone. Hydromorphone was associated with a significantly lower risk of both adverse events (0.60 [95% CI 0.39 to 0.90]) and serious adverse events (0.21 [95% CI 0.06 to 0.69) compared to diacetylmorphine.[13] For these reasons, either medication can be considered a reasonable choice, based on availability, patient choice, and prescriber judgement.

Recommendation 3	
Injectable opioid agonist treatment should be provided as an open-ended treatment, with decisions to transition to oral OAT made collaboratively with the patient.	
Quality of Evidence: **Low**	Strength of Recommendation: **Strong**
Remarks: The quality of evidence is rated low due to the low number of studies evaluating the impact of pre-determined treatment end dates. It was decided that this recommendation should be strong despite the low quality of evidence, due to the risk associated with fentanyl-contaminated illicit opioid use and its alignment with a recommendation from the World Health Organization that opioid agonist treatment be provided as an open-ended treatment.[153]	

Evidence Summary:

A loss of treatment benefit when prescription diacetylmorphine treatment was discontinued at a predetermined end date has been found in two post-randomized controlled trial observational cohorts.[42,43] Both of these studies found an increase in street heroin use post treatment end to levels comparable to that of the control group. One study found a rapid deterioration in 82% (94/115) of responders in the diacetylmorphine group two months after treatment discontinuation, with mean scores on the constituent scales of the multi-domain outcome index returning to pre-treatment levels,[43] while the other showed a significant increase of street heroin use in the diacetylmorphine group three months after treatment discontinuation (p=0.005, mean number of days of heroin use in past month=8 days at 12 months, mean=14 days at 15 months).[42] Another study compared individuals who voluntarily transitioned from injectable diacetylmorphine to oral methadone prior to the completion of a randomized controlled trial against those who were involuntarily transitioned at the end of the 12-month trial, and found that the mean prior 30 days of illicit heroin use was higher in the involuntary group than the voluntary group at 24 months (adjusted mean difference: -5.58 [95% CI -11.62 to 0.47]) and treatment retention was significantly lower (adjusted odds ratio: 5.55 [95% CI 1.11 to 27.81]).[154]

APPENDIX 4—DSM-5 CLINICAL DIAGNOSTIC CRITERIA FOR OPIOID USE DISORDER

Clinical Diagnostic Criteria for Opioid Use Disorder		
1	Opioids are often taken in larger amounts or over a longer period than was intended	The presence of at least 2 of these symptoms indicates an OUD The severity of the OUD is defined as: **MILD:** The presence of 2 to 3 symptoms **MODERATE:** The presence of 4 to 5 symptoms **SEVERE:** The presence of 6 or more symptoms
2	There is a persistent desire or unsuccessful efforts to cut down or control opioid use	
3	A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects	
4	Craving or a strong desire to use opioids	
5	Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home	
6	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids	
7	Important social, occupational, or recreational activities are given up or reduced because of opioid use	
8	Recurrent opioid use in situations in which it is physically hazardous	
9	Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.	
10	Tolerance*, as defined by either of the following: a) Need for markedly increased amounts of opioids to achieve intoxication or desired effect b) Markedly diminished effect with continued use of the same amount of opioid	
11	Withdrawal*, as manifested by either of the following: a) Characteristic opioid withdrawal syndrome b) Same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms	
*Patients who are prescribed opioid medications for analgesia may exhibit these two criteria (withdrawal and tolerance), but would not necessarily be considered to have a substance use disorder.		

References:

American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-5™*.

5th ed. Arlington, VA: American Psychiatric Publishing, Inc.

APPENDIX 5: PRE-AND POST-INJECTION ASSESSMENT

Patient Name: _____

Assessment Date and Time: _____

Yes	No	
☐	☐	Severely anxious or agitated
☐	☐	Dyskinetic
☐	☐	Overly sedated
☐	☐	Slurred speech
☐	☐	Smells of alcohol
☐	☐	Breathing normally If no, respiration rate: _____ Pasero Opioid-induced Sedation Scale[155] (POSS) level: _____
☐	☐	Breathalyzer required If yes, breathalyzer reading: _____

Notes:

_____

_____

_____

Assessment completed by: _____

The pre- and post-injection assessments[y] are completed by a qualified health professional or other trained staff if supervised by a health professional 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 or diacetylmorphine. 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-minute observation period post dose.

y The pre- and post-intake assessment protocol has been adapted from the protocol used at Providence Health Care's Crosstown Clinic in Vancouver, BC.

Pre-Injection Assessment

A qualified health professional or other appropriately trained staff, including peer staff, if supervised by a qualified health professional 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 3 below.

Table 3: Pre-Injection Assessment

Patient Name: _____

Assessment Date and Time: _____

Yes	No	
☐	☐	Severely anxious or agitated
☐	☐	Dyskinetic
☐	☐	Overly sedated
☐	☐	Slurred speech
☐	☐	Decreased respiration rate
☐	☐	Breathing normally If no, respiration rate: _____
		Pasero Opioid-induced Sedation Scale[155] (POSS) level: _____

Notes:

_____

_____

_____

Assessment completed by: _____

If initial assessment results in suspicion of recent use of psychoactive substances, the staff member should discuss with the patient whether they have consumed illicit drugs (including any non-prescribed pharmaceutical drug) or alcohol. Where observation warrants further assessment (e.g., slurred speech, unsteady gait, smells of alcohol), a health professional or other staff if supervised by a health professional (physician, nurse practitioner, Registered Nurse, Registered or Licensed Practical Nurse, Registered Psychiatric Nurse, or pharmacist) trained to administer breathalyzer testing should 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 sedation did occur at the last dose and this is thought to be due to the prescribed iOAT medication, the prescriber should be consulted before further doses are administered. The prescriber should reduce the dose, typically starting with the last dose that did not cause sedation. The post-dose evaluation duration may need to be extended. If this lowered dose is tolerated, further up-titration may then be pursued (if needed), typically in smaller increments. If sedation was the result of one-time illicit substance use and the patient presents for their next dose alert and the pre-dose assessment does not indicate sedation, there may not need to be a dose adjustment. If the patient continues to experience sedation, their dose may need adjustment and their ongoing substance use should be managed. See Ongoing Substance Use.

If a prolonged absence has occurred (more than five days), the patient should be re-titrated following the process outlined in Appendix 7.

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 minutes after they inject their medication. Qualified health professionals or other trained staff if supervised by a health professional (physician, nurse practitioner, Registered Nurse, Registered or Licensed Practical Nurse, Registered Psychiatric Nurse, or pharmacist) can use this period to observe and engage with patients.

After 15 minutes has elapsed, a qualified health professional or other trained staff if supervised by a health professional (physician, nurse practitioner, Registered Nurse, Registered or 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 4 below.

Table 4: Post-Injection Assessment

After a minimum of 15 minutes, once a patient is deemed fit to leave the clinic (i.e., 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 15-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 dose 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,[155] using the POSS scale provides a consistent way to measure sedation and provide follow-up when needed.

Table 5 provides an adapted version of the Pasero Opioid-induced Sedation Scale (POSS) with appropriate actions for each level of sedation.

Table 5: 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 6: HEALTH CARE PROVIDER ADMINISTRATION OF INJECTABLE MEDICATION

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 health care providers to ensure continuity of care. In some circumstances, there may be other clinical or psychosocial indications for health care provider administration of injectable medication, in order to enable a client with specific needs to access iOAT. In these cases, and depending on the model of care and jurisdiction, health care providers may provide subcutaneous or intramuscular (IM) injections in the deltoid, ventrogluteal, or dorsogluteal muscles. Standard protocols for IM injection including rotating sites and matching site to volume of medication should be followed. Nurses may be able to provide intravenous (IV) injection when requested by the patient and determined appropriate. Regional differences may exist in terms of what medications can be administered by IV injection by various nursing professionals. Where possible, institutional policies should be developed to outline appropriate orders required, standard protocols for IV injection, and necessary staff education.

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., disability or mobility issues). It is recommended that clinical judgment be used in these situations to determine if iOAT with health care provider administration is the most appropriate treatment.

APPENDIX 7: TITRATION PROCESS

The following outlines the recommended titration process for iOAT.

As with the general process for iOAT, doses are self-administered intravenously, intra-muscularly, or subcutaneously under supervision, with physicians, nurse practitioners, Registered Nurses, Registered Psychiatric Nurses, Licensed Practical Nurses, and, in some jurisdictions, pharmacists able to administer injectable medications when clinically indicated (see Appendix 6).

At any time during the titration period, a physician, nurse practitioner, nurse or (where applicable) pharmacist (in collaboration with the prescribing physician or nurse practitioner) 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. The most predictable, though rare, side effect during titration is oversedation, which is manageable with dose reductions and a modified (slower) titration schedule.

For iOAT programs that do not have capacity for titrations 7 days a week, it is recommended that the titration process be started between Monday and Wednesday to avoid the need for dose increases on the weekend.

The prescriber may adjust the dosage once per day, 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 for hydromorphone; 400mg/dose and/or 1000mg/day for diacetylmorphine). Dose increases are discouraged on weekends and holidays if the prescriber is not available.

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. Three doses per day is better studied; however, clinical practice in British Columbia has shown that many individuals do well on two doses per day.

Note: For the supervised 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.

Hydromorphone Titration Protocol 1—Three Doses Per Day

Day 1 (Total Dose Range=60-90mg)

Dose 1: Give 10mg, wait 15 minutes. If no intoxication, give an additional 10mg based on clinical judgment and discussion with patient. Observe for 15 minutes after additional dose. **Total possible dose=20mg.**

Minimum 3 hours between dose 1 and dose 2.

Dose 2: If earlier doses were well tolerated, give 20mg. Wait 15 minutes. If no intoxication, give an additional 10mg based on clinical judgment and discussion with patient. Observe for 15 minutes after additional dose. **Total possible dose=30mg.**

Minimum 3 hours between dose 2 and dose 3.

Dose 3: If earlier doses were well tolerated, give 30mg. Wait 15 minutes. If no intoxication, give an additional 10mg based on clinical judgment and discussion with patient. Observe for 15 minutes after additional dose. **Total possible dose=40mg.**

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

Day 2 (Total Dose Range=150-180mg)

Dose 1: Administer 40mg, wait 15 minutes. If no intoxication, give an additional 10mg based on clinical judgment and discussion with patient. Observe for 15 minutes after additional dose. **Total possible dose=50mg.**

Minimum 3 hours between dose 1 and dose 2.

Dose 2: Administer 50mg, wait 15 minutes. If no intoxication, give an additional 10mg based on clinical judgment and discussion with patient. Observe for 15 minutes after additional dose. **Total possible dose=60mg.**

Minimum 3 hours between dose 2 and 3.

Dose 3: Administer 60 mg, wait 15 minutes. If no intoxication, give an additional 10mg based on clinical judgment and discussion with patient. Observe for 15 minutes after additional dose. **Total possible dose=70mg.**

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

Day 3 (Total Dose Range=240-260mg)

Dose 1: Administer 70mg, wait 15 minutes. If no intoxication, give an additional 10mg based on clinical judgment and discussion with patient. Total possible dose=80mg.

Minimum 3 hours between dose 1 and 2.

Dose 2: Administer 80mg, wait 15 minutes. If no intoxication, give an additional 10mg based on clinical judgment and discussion with patient. Total possible dose=90mg.

Minimum 3 hours between dose 2 and 3.

Dose 3: Administer 90mg. Observe for 15 minutes.

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

Table 6 below summarizes the dosages used during the induction process for quick reference.

Table 6: Hydromorphone Induction Dosage Chart—3 Doses Per Day

Dose #	Dose Administered	Additional Dose* (if appropriate)
Day 1		
1	10mg	10mg
2	20mg	10mg
3	30mg	10mg
Total	**60-90mg**	
Day 2		
1	40mg	10mg
2	50mg	10mg
3	60mg	10mg
Total	**150-180mg**	
Day 3		
1	70mg	10mg
2	80mg	10mg
3	90mg	--
Total	**240-260mg**	

**Wait 15 minutes after initial dose. If no intoxication, give additional dose based on clinical judgment and discussion with patient.*

Hydromorphone Titration Protocol 2—Two Doses Per Day

For patients who will be receiving two doses of hydromorphone per day, at the discretion of their prescriber, patients may be titrated onto a two-dose schedule. A suggested titration schedule follows. Those needing additional guidance should consult an experienced iOAT provider.

Day 1 (Total Dose Range=60-120mg)

Dose 1: Give 15mg, wait 15 minutes. If no intoxication, give an additional 30mg based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Total possible dose=45mg.**

Minimum 3 hours between injections.

Dose 2: If earlier doses were well tolerated, give 45mg. Wait 15 minutes. If no intoxication, give 30mg more based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Total possible dose=75mg.**

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

Day 2 (Total Dose Range=180-235mg)

Dose 1: Administer 75mg, wait 15 minutes. If no intoxication, give 30mg more based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Total possible dose=105mg.**

Minimum 3 hours between injections.

Dose 2: Administer 105mg, wait 15 minutes. If no intoxication, give 25mg more based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Total possible dose=130mg.**

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

Day 3 (Total Dose Range=270-290mg)

Dose 1: Administer 130mg, wait 15 minutes. If no intoxication, give 10mg more based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Total possible dose=140mg.**

Minimum 3 hours between injections.

Dose 2: Administer 140mg, wait 15 minutes. If no intoxication, give 10mg more based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Total possible dose=150mg.**

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

As each patient goes through the titration process, they should stop at the dose where they are comfortable and have alleviated withdrawal and cravings. This will be their ongoing dose. If the patient is oversedated post-injection, the prescriber should be consulted to determine if the next dose should be lowered and to assess any changes in the patient's health status prior to their next dose. The prescriber may order a lower dose at the next injection, with the option to continue to titrate up depending on how the new dose is tolerated.

Table 7 below summarizes the dosages used during the induction process for quick reference.

Table 7: Hydromorphone Induction Dosage Chart—2 Doses Per Day

Dose #	Dose Administered	Additional Dose* (if appropriate)
Day 1		
1	15mg	30mg
2	45mg	30mg
Total	**60-120mg**	
Day 2		
1	75mg	30mg
2	105mg	25mg
Total	**180-235mg**	
Day 3		
1	130mg	10mg
2	140mg	10mg
Total	**270-290mg**	
**Wait 15 minutes after initial dose. If no intoxication, give additional dose based on clinical judgment and discussion with patient.*		

Alternate Titration Protocols

Clinical experience from British Columbia, where fentanyl has infiltrated the illicit opioid supply, has shown that the above recommended titration protocols may be insufficient in ameliorating withdrawal symptoms and cravings in some individuals who have developed a very high opioid tolerance due to fentanyl. For this reason, titration protocols have been adapted by some iOAT programs. Two alternate titration protocols are offered below (a three doses per day and a two doses per day protocol), which were developed according to clinical expertise by iOAT providers in Vancouver, BC. Although these alternate protocols have been used in clinical practice, it should be understood that they have not been rigorously evaluated for safety or their impact on retention.

Table 8: Alternate Hydromorphone Induction Dosage Chart —3 Doses Per Day

Dose #	Dose Administered	Additional Dose* (if appropriate)
Day 1		
1	20mg	20mg
2	40mg	20mg
3	60mg	20mg
Total	**120-180mg**	
Day 2		
1	70mg	20mg
2	90mg	20mg
3	110mg	20mg
Total	**270-330mg**	
Day 3		
1	130mg	--
2	130mg	--
3	130mg	--
Total	**390mg**	

**Wait 15 minutes after initial dose. If no intoxication, give additional dose based on clinical judgment and discussion with patient.*

Table 9: Alternate Hydromorphone Induction Dosage Chart —2 Doses Per Day

Dose #	Dose Administered	Additional Dose* (if appropriate)
Day 1		
1	30mg	30mg
2	60mg	30mg
Total	**90-150mg**	
Day 2		
1	90mg	30mg
2	130mg	--
Total	**220-250mg**	
**Wait 15 minutes after initial dose. If no intoxication, give additional dose based on clinical judgment and discussion with patient.*		

Diacetylmorphine Titration Protocol 1—Three Doses Per Day

Day 1 (Total Dose Range: 135-225mg)

Dose 1: Give 15mg, wait 15 minutes. If no intoxication, give an additional 30mg based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Total possible dose=45mg.**

Minimum 3 hours between dose 1 and dose 2.

Dose 2: If earlier doses were well tolerated, give 45mg. Wait 15 minutes. If no intoxication, give an additional 30mg based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Total possible dose=75mg.**

Minimum 3 hours between dose 2 and dose 3.

Dose 3: If earlier doses were well tolerated, give 75mg. Wait 15 minutes. If no intoxication, give an additional 30mg based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Total possible dose=105.**

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

Day 2 (Maximum Day 2 Total Dose=450mg)

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 15 minutes. If no intoxication, give an additional 30mg based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Maximum total dose=120mg.**

Minimum 3 hours between dose 1 and dose 2.

Dose 2: Administer the maximum tolerated amount of Dose 1 (up to a total of 120mg). Wait 15 minutes. If no intoxication, give an additional 30mg based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Maximum total dose=150mg.**

Minimum 3 hours between dose 2 and dose 3.

Dose 3: Administer the maximum tolerated amount of Dose 2 (up to a total of 150mg). Wait 15 minutes. If no intoxication, give an additional 30gm based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Maximum total dose=180mg.**

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

Day 3 (Maximum Day 3 Total Dose=540mg)

Administer the maximum tolerated amount at Dose 3, Day 2 for each of the 3 doses on Day 3. After consulting with the prescriber, 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, if prescribers are not available. **Maximum individual dose=180mg.**

Table 10: Diacetylmorphine Induction Dosage Chart—3 Doses Per Day

Dose #	Dose Administered	Additional Dose* (if appropriate)
Note: *This is a general protocol which must be personalized to each individual per clinical judgment.*		
Day 1		
1	15mg	30mg
2	45mg	30mg
3	75mg	30mg
Total	**135-225mg**	
Day 2		
1	40% of total daily dose at Day 1	30mg
2	Maximum tolerated Day 2 Dose 1 dose	30mg
3	Maximum tolerated Day 2 Dose 2 dose	30mg
Total	**Maximum 450mg**	
Day 3		
1	Maximum tolerated amount at Day 2 Dose 3	--
2	Maximum tolerated amount at Day 2 Dose 3	--
3	Maximum tolerated amount at Day 2 Dose 3	--
Total	**Maximum 540mg**	
**Wait 15 minutes after initial dose. If no intoxication, give additional dose based on clinical judgment and discussion with patient.*		

Diacetylmorphine Titration Protocol 2—Two Doses Per Day

For patients who will be receiving two doses of diacetylmorphine per day, at the discretion of their prescriber, patients may be titrated onto a two-dose schedule. A suggested titration schedule follows. Those needing additional guidance should consult an experienced iOAT provider.

Day 1 (Total Dose Range=120-240mg)

Dose 1: Give 30mg, wait 15 minutes. If no intoxication, give an additional 60mg based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Total possible dose=90mg.**

Minimum 3 hours between injections.

Dose 2: If earlier doses were well tolerated, give 90mg. Wait 15 minutes. If no intoxication, give 60mg more based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Total possible dose=150mg.**

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

Day 2 (Total Dose Range=260-360mg)

Dose 1: Administer 100mg, wait 15 minutes. If no intoxication, give 60mg more based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Total possible dose=160mg.**

Minimum 3 hours between injections.

Dose 2: Administer 160mg, wait 15 minutes. If no intoxication, give 40mg more based on clinical judgment and discussion with patient. Observe for 15 minutes after second dose. **Total possible dose=200mg.**

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

Day 3 (Total Dose Range=400mg)

Doses 1 and 2 on Day 3 will often be the ongoing final dose for the patient. If all previous doses were well tolerated, doses on Day 3 should be 200mg

As each patient goes through the titration process, they should stop at the dose where they are

comfortable and have alleviated withdrawal and cravings. This will be their ongoing dose. If the patient is oversedated post-injection, the prescriber should be consulted to determine if the next dose should be lowered and to assess any changes in the patient's health status prior to their next dose. The prescriber may order a lower dose at the next injection, with the option to continue to titrate up depending on how the new dose is tolerated.

Table 11: Diacetylmorphine Induction Dosage Chart—2 Doses Per Day

Dose #	Dose Administered	Additional Dose* (if appropriate)
Day 1		
1	30mg	60mg
2	90mg	60mg
Total	**120-240mg**	
Day 2		
1	100mg	60mg
2	160mg	40mg
Total	**260-360mg**	
Day 3		
1	200mg	--
2	200mg	--
Total	**400mg**	
**Wait 15 minutes after initial dose. If no intoxication, give additional dose based on clinical judgment and discussion with patient.*		

Alternate Titration Protocols

Due to the higher risk of adverse events and sedation with diacetylmorphine compared to hydromorphone,[13] accelerated titration protocols for diacetylmorphine are not recommended.

Co-Prescription of Oral OAT

Oral OAT is frequently co-prescribed with iOAT in order to prevent withdrawal and cravings between iOAT doses, particularly overnight during the longest between-dose period, as the injectable medications are relatively short-acting. In the randomized controlled trials studying supervised injection diacetylmorphine, methadone was co-prescribed in two trials,[43,156] and available for various reasons (to

prevent withdrawal over-night, for travel, to reduce attendance to one or two times per day) in five trials.[13,14,140,157,158] Where listed, the average methadone dose ranged from 8mg to 60mg per day.[13,43,140,156]

A dose of oral OAT (i.e., SROM or methadone) may be taken daily under supervision to bridge between doses, with the longest gap between doses occurring overnight. Caution and safety should guide co-prescription, while working to ensure patient comfort. Nurses and/or pharmacists should assess the patient each day during the titration period to ensure the co-prescribed oral OAT is appropriately dosed. Co-prescribed oral OAT can be given at any time, based on the patient's comfort (for example, with the first injection of the day, with the last injection of the day, or separately in the evening).

There is insufficient data to guide specific target dosing of supplemental oral OAT, however, it should be guided by patient preference and clinical effect. Induction of co-prescribed methadone should follow the process outlined in CRISM's National Guideline for the Clinical Management of Opioid Use Disorder. Guidance on induction of SROM can be found in the BCCSU's A Guideline for the Clinical Management of Opioid Use Disorder. Oral OAT may be started in advance if practical matters require waiting to start iOAT, at the same time as iOAT induction, or after a patient has been titrated onto iOAT.

An example titration chart of both hydromorphone and methadone follows in Table 12.[z] This chart is informed by clinical expertise and represents one possible way of co-prescribing methadone with hydromorphone, in a two-doses per day setting in which the patient is still experiencing discomfort and cravings after the initial three-day titration.

Table 12: Example Hydromorphone and Methadone Co-Prescription Initiation

Day	Dose	Hydromorphone Total Dose	Methadone dose
1	1	45mg	30mg
	2	75mg	--
2	1	105mg	30mg
	2	130mg	--
3	1	140mg	30mg
	2	150mg	--
4	1	160mg	30mg
	2	160mg	--
5	1	170mg	40mg
	2	170mg	--

z **Note:** Different provinces and jurisdictions have different recommendations for methadone titration. See CRISM's National Guideline for the Clinical Management of Opioid Use Disorder.

APPENDIX 8: EXAMPLE DOSE REDUCTION PROTOCOL

For individuals who have stabilized on a maintenance dose who miss 6 consecutive doses or 2 days (whichever is first) but fewer than 9 doses or 3 days (whichever is first), their dose should be reduced by 1/3 (one-third). Each subsequent dose can be increased by 25mg until they are back at their regular dose.[aa]

aa Adapted from PHS Community Services Society in Vancouver, BC.

APPENDIX 9: 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 is clinically contraindicated). Ideally, travel is planned in advance, allowing for a slow titration from iOAT to oral OAT following province-specific guidelines, which can be found in CRISM's National 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 SROM, with daily witnessed ingestion, for its improved safety profile, including significantly less variability in required dosage.

IMPORTANT SAFETY NOTE: The conversion table below is approximate and clinical judgment should guide conversions, including **reducing the target dose 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 **and should follow standard principles for safe conversions between injectable and oral opioid medication routes of administration, as this table outlines approximate equianalgesic doses only for IV conversions between HM and DAM**.

When possible, the converted travel dose should be trialled for a few days prior to travel to prevent destabilization.

Patients should be provided with take-home naloxone kits and training on how to administer naloxone. It is ideal to have family or friends who 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.

Most patients do well on doses of methadone between 60-120mg per day.[33] To ensure patient safety, it is recommended that this target dose range not be exceeded and that a maximum dose of 1200mg SROM not be exceeded.

Table 13: Conversion Table[bb]

Injection Diacetylmorphine (mg)	Injection Hydromorphone (mg)	SROM (mg)	Oral Methadone (mg)[cc]
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

bb 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

cc If possible, a gradual titration crossover is recommended. These methadone conversion doses are safe for a single-dose replacement or continuously for several days.

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	351-530	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

APPENDIX 10: STRATEGIES FOR TRANSITIONING BETWEEN OR DE-INTENSIFYING TREATMENT

De-intensification of treatment may be appropriate and/or required for one of four 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, see iOAT Operations Guidance). When switching models of care, the prescriber should ensure that existing psychosocial supports will remain in place, if possible. 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). The final reason a patient may require de-intensification of treatment is if they have been convicted of a crime and face a period of incarceration.

This guideline 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. Strategies for transitioning between hydromorphone and diacetylmorphine (and the reverse) are also provided below.

Transition from Hydromorphone to Diacetylmorphine

Transition from hydromorphone to diacetylmorphine (using a 1:2 [HDM:DAM] potency ratio with a 25% dose reduction to account for incomplete cross tolerance, see Conversion Table in Appendix 9) will be subject to availability of diacetylmorphine (see iOAT Operations Guidance). Patients and prescribers may collaboratively choose to transition to diacetylmorphine if the patient is not benefitting sufficiently or experiencing unacceptable side effects. It should be noted that diacetylmorphine may pose an increased risk of adverse events (e.g., histamine reactions, seizures, and overdose) compared to injectable hydromorphone.[13] See Appendix 11 for a table of serious side effects for both medications. See Medication Selection and Preparation for considerations on initial selection of iOAT medication.

Transition from Diacetylmorphine to Hydromorphone

Patients and prescribers may collaboratively choose to transition from diacetylmorphine to hydromorphone (using a 2:1 [DAM:HDM] potency ratio with a 25% dose reduction to account for incomplete cross tolerance, see Conversion Table in Appendix 9) if the patient is not benefitting sufficiently

or experiencing unacceptable side effects. It should be noted that diacetylmorphine may pose an increased risk of adverse events (e.g., histamine reactions, seizures, and overdose) compared to injectable hydromorphone.[13] See Appendix 11 for a table of serious side effects for both medications. See Medication Selection and Preparation for considerations on initial selection of iOAT medication.

Transition from Hydromorphone or Diacetylmorphine to Methadone

Transition from injectable hydromorphone to oral methadone (see Conversion Table in Appendix 9) 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. Province-specific guidelines for methadone induction should be followed and can be found in CRISM's National 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.

Transition from Hydromorphone or Diacetylmorphine to Slow-Release Oral Morphine

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 or diacetylmorphine dose while simultaneously up-titrating the SROM dose. One titration approach would start with a 10% hydromorphone/diacetylmorphine dose decrease per week, with concurrent increase in SROM. The speed of transition should be guided by the patient's goals and subjective experiences (e.g., cravings, withdrawal symptoms, sleep). General induction and dosing recommendations for SROM can be found in the BC Centre on Substance Use'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.[159,160] Slow-release oral morphine 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 SROM in the treatment of OUD, including as a supplement to ongoing iOAT, is provided below.

A 2014 two-phase study investigating the safety and efficacy of SROM compared to methadone in adults with moderate to severe OUD 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 were offered 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.[161] Slow-release oral morphine's non-inferiority[161] and favourable side effect profile compared to methadone for the treatment of OUD[44] (specifically its lack of association with a prolonged QTc and subsequent risk for arrhythmia and fewer drug-drug interactions) make it a suitable alternative to methadone.

For patients receiving iOAT and supplementary oral OAT, there is some research evidence that switching from supplementary methadone to supplementary SROM 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 SROM with no planned decrease in their iOAT dose.[162] 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.[162] 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.[162] Patients also reported fewer cravings and improved sleep and quality of life after switching from supplementary methadone to SROM. Although more research is needed, this preliminary study suggests that supplementary SROM may be a viable alternative to methadone, and may have advantages in patients wishing to reduce their daily iOAT dose and/or those considering transition to oral OAT. It should be highlighted that this is a small observational study and additional research is needed in order to optimize transitions from iOAT to SROM.

Transition from Hydromorphone or Diacetylmorphine to Buprenorphine/Naloxone

There is currently very limited literature on transitioning from iOAT to buprenorphine/naloxone.[163] 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.[163] Additionally, a small number of patients have been successfully transitioned in

Vancouver, both in in-patient withdrawal management facilities, following the BC-specific induction guidelines which can be found in CRISM's National Guideline for the Clinical Management of Opioid Use Disorder, and using the Bernese method in an outpatient setting. Transition to buprenorphine/naloxone should follow the same approach used for transitioning patients from any high-dose short-acting opioids onto buprenorphine/naloxone. Province-specific guidance can be found in CRISM's National 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 health care 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 9, with a 25-30% 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.

De-Intensification of Treatment Due to Incarceration

Patients who have been convicted of a crime and face a period of incarceration must be transitioned to a suitable oral OAT option prior to, or as quickly as possible following, their entry into the correctional system. The medication-specific transition recommendations above should be followed. If transition to oral OAT is not possible prior to incarceration, the community prescriber should contact the most responsible physician (MRP) in the correctional facility to inform them that the patient is on iOAT and will thus have a high opioid tolerance and make recommendations for the management of OUD and transition to oral OAT while the patient is subject to a custodial environment.

APPENDIX 11: COMMON AND SERIOUS SIDE EFFECTS

Hydromorphone and diacetylmorphine can cause the same side effects as other opioids, including sedation, nausea and vomiting, constipation, miosis, flushing, and pruritus.[164] The 3-glucoronide metabolite of hydromorphone has been implicated in neuroexcitation symptoms (e.g., tremor, myoclonus, cognitive dysfunction).[165] In addition, long-term opioid use, including iOAT, may lead to abnormalities in the endocrine system, mainly affecting the gonadal axis and leading to hypogonadism.[22,23] In line with this, low testosterone levels and erectile dysfunction have been associated with long-term opioid use (including oral OAT) in males,[24] and menstrual disturbances in females.[22] Osteoporosis and reduced bone mineral density can also result from hypogonadism. Specific serious side effects noted in clinical trials are provided in the table below.

Diacetylmorphine may pose an increased risk of other adverse events (e.g., histamine reactions, seizures, and overdose) compared to injectable hydromorphone[13] and oral methadone.[11,12] 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.[12] 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.[14] 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.[38]

Table 14—Serious Adverse Events Related to the Study Medications

Diacetylmorphine[13,14]	Hydromorphone[13,14,166]
• Sepsis and other infections • Seizures • Diseases of the respiratory system • Abscesses and cellulitis • Fractures • Overdose	• Respiratory depression • Abscesses and cellulitis • Suicidal ideation • Overdose

APPENDIX 12: URINE DRUG TESTING

Urine drug testing (UDT) can be used to help guide patient care, to ensure patients are aware of which substances they are ingesting if using illicit substances, and to start a conversation on harm reduction and safety. Unlike with oral OAT, where regular and random UDT are considered standard of care, regular and mandatory call-back UDT are not considered standard care for iOAT, due to both the low risk of diversion and the high frequency of contact with care providers.

Other than the initial UDTs performed to confirm illicit opioid use, there is no required number of UDTs for iOAT programs. Point-of-care UDT may be useful for providing immediate feedback to patients and for making prompt treatment decisions, when potentially harmful substances are detected, as well as monitoring trends. 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. Given the public health emergency in parts of Canada, point-of-care tests should include fentanyl.

Given the risk of fentanyl contamination in illicit substances, including stimulants and other non-opioids, it is recommended that prescribers discuss drug checking with patients and the option for urine or take-home fentanyl testing.

It is emphasized that UDT should not be used punitively and should not lead to discharge for ongoing stimulant or opioid use. Patients who are showing signs of instability or disclose ongoing illicit substance use may benefit from using UDT to guide more intensive follow-up and reassessment. Following discussion with the patient about any underlying issues contributing to treatment instability, prescribers can consider adjusting iOAT dose, prescribing a supplemental daily dose of oral methadone or SROM, or adjusting supplemental oral OAT 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, prescribers and patients may need to consider alternative treatment options or care settings, such as the comprehensive and dedicated supervised iOAT model of care (see iOAT Operations Guidance).

APPENDIX 13: RESPONDING TO DOSE INTOLERANCES

Each iOAT program should have its own protocols in place for responding to dose intolerances and other adverse events, including required documentation. The following provides general guidance on how to respond to dose intolerances, adapted from the BC Centre for Disease Control's Administration of Naloxone Decision Support Tool. This guidance can be adapted to local practice setting and should be tailored to each specific site.

Clinical Features of Dose Intolerance:

Signs and symptoms of opioid intoxication (dose intolerance) include:

- Decreased respiratory rate or absence of respirations. A respiratory rate of fewer than 10-12/min is the best clinical predictor of opioid intoxication
- Oxygen saturation of <90% on room air
- Gurgling or snoring-type sounds
- Slow, erratic, or absent heart rate
- Vomiting
- Altered mental status (minimally responsive to unresponsive)
- Constricted (pinpoint) pupils (however, the presence of pinpoint pupils alone is not sufficient to diagnose opioid intoxication)
- Cold and clammy skin (may appear cyanotic [blueish], especially around the lips or nailbeds, in individuals with lighter skin; may appear grayish or ashen in individuals with darker skin)

Assessment

Assessment should be rapidly performed to determine if dose intolerance is suspected and whether naloxone administration is indicated. The assessment should also look for factors that might complicate the management of dose intolerance and necessitate rapid referral to a hospital setting. The pre-dose assessment may identify complicating factors.

Information on Naloxone HCL

Initial dose: 0.4mg IM/SC/IV

Subsequent dose: 0.4mg, 0.4 mg

Each dose should be administered 3–5 minutes apart.

Naloxone can be given until EMS arrives or individual is able to breathe on their own.

Clinical judgment to discontinue naloxone administration should take into account the number of doses given, time elapsed since administration of first dose, client responsiveness, and presenting scenario.

Onset: IV=less than 2 minutes; IM/SC=3–5minutes

Duration of action: 20 to 90 minutes

Side effects: Abrupt reversal of opioid depression may result in:

CNS	CVS	Emotional State
Excitation	Tachycardia Arrhythmias Hypertension	Agitated Irritable Confused/startled
GI	**Skin**	**Other**
Nausea Diarrhea Vomiting Cramping	Sweating Tremulousness	Pain/pain crisis (if opioid used for pain management)

Special considerations: An initial dose of 0.2mg IM/SC may be administered in advanced practice settings where extra supports (e.g., supplemental oxygen, pulse oximetry) are available and capacity exists for continued resuscitation and monitoring.

In these advanced practice settings, 911 may not necessarily be required, if adequate staffing and training support the capacity to continually monitor individuals and resuscitate and provide care as needed.

Naloxone's duration of action (20–90 minutes) is shorter than that of all opioids. Thus, individuals should be observed until the opioid effect has worn off.

Management

Immediately begin management if assessment indicates a dose intolerance. Naloxone should be used alongside the principles of basic life support along with cardiopulmonary resuscitation for trained individuals (CPR; compressions plus ventilation).

The goal of naloxone administration is to:

- Achieve adequate spontaneous ventilation (RR>10/min)
- Protect the airway
- Not precipitate acute withdrawal symptoms

Clinical Features of Acute Opioid Withdrawal

Following naloxone administration, acute opioid withdrawal may occur. Signs and symptoms of opioid withdrawal include:

- Anxiety, irritability, aggressive behaviour
- Dilated pupils
- Tachycardia (increased heart rate)
- Diarrhea
- Nausea and vomiting
- Abdominal cramps
- Sweating, chills, goosebumps
- Muscle and joint pain
- Tremulousness

Opioids should not be given for acute treatment of opioid withdrawal following treatment for a dose intolerance.

Follow-Up Care

The effects of naloxone wear off after 20–90 minutes, while the effects of opioids last much longer. Individuals should be monitored for a minimum of 2–3 hours following the last dose of naloxone. If necessary, provide additional doses of naloxone. Advise clients to not use more opioids for a minimum of 2–3 hours following the last dose of naloxone.

APPENDIX 14: SAMPLE TREATMENT AGREEMENT AND CONSENT FORM

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.
- ☐ Diacetylmorphine for the treatment of opioid use disorder.

☐ While I am receiving hydromorphone/diacetylmorphine treatment, I will not obtain opioid prescriptions or other psychoactive medications (e.g., sleeping pills or pain medication) from other doctors, nurse practitioners, clinics, or elsewhere. If I need opioids for the treatment of acute pain, I will inform the prescriber that I am on iOAT and will agree to communication between this prescriber and my iOAT prescriber to help coordinate safety.

☐ For my safety, I give consent to my hydromorphone/diacetylmorphine prescriber to communicate with my pharmacist and any other physicians or nurse practitioners currently or previously involved in my care, and to check my province's prescription monitoring program.

☐ I will work with my treatment team to develop a treatment plan and set goals. We will review them regularly and change as needed.

☐ In addition to hydromorphone/diacetylmorphine, I can participate in counseling or peer-support groups and other programs as part of my treatment plan. My treatment team will give me information about the options and programs available in my community.

☐ My treating team may include some or all of the following: prescriber, nurses, social worker, pharmacist, and others. My treating team will work collaboratively and respectfully with me in planning treatment and providing care.

☐ I can expect confidentiality about my treatment from my treatment team and other health care providers. My personal information will not be shared except with other health care providers as I agreed to above. I understand that confidentiality will need to be breached if I am a danger to myself or others or if a child is at risk.

☐ 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/diacetylmorphine 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 clinically stable), my prescriber and I will discuss the reasons for missed doses.

☐ 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.

☐ If I am assessed to be intoxicated during the pre-injection assessment, my dose will be postponed or withheld for my safety.

☐ I have discussed potential side effects and adverse events (seizure, overdose, constipation, pruritus [severe skin itching], hypogonadism [hormonal abnormalities that can lead to low testosterone levels, erectile dysfunction, and menstrual disturbances], and sleep apnea) associated with iOAT with my health care provider and we have agreed on plans to mitigate risk.

☐ I will not be cut off from treatment. If hydromorphone/diacetylmorphine 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 when asked.
- ☐ 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/diacetylmorphine 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/diacetylmorphine 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.
- ☐ Treat staff and other patients with respect.

Patient Identified Goals

- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____

Treating Team 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/diacetylmorphine.
- ☐ Information and resources to support psychosocial treatment interventions and supports will be provided to the patient.
- ☐ The provincial prescription drug monitoring program was reviewed (where applicable) 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:_____

Staff member's signature:_____ Date:_____

APPENDIX 15: SUPPLEMENTARY RESOURCES

A variety of supplementary resources are available on the CRISM website. These include:

- Example pre-printed orders
- Frequently asked questions for patients and their families
- Case studies
- An example treatment plan

The BC Centre on Substance Use provides two online training opportunities open to individuals across Canada:

The Provincial Opioid Addiction Treatment Support Program, which provides training for nurse practitioners and physicians to diagnose and treat opioid use disorder using evidence-based treatments along a continuum of care, including iOAT.

The Addiction Care and Treatment Online Course, which provides addiction medicine training for family physicians, specialists, nurses, nurse practitioners, pharmacists, and other healthcare practitioners involved in addiction care and treatment.

Glossary

Addiction treatment: In this document, addiction treatment refers to ongoing or continued care for substance use disorder(s) delivered by a trained care provider. For opioid use disorder, this could include evidence-based pharmacological treatment (opioid agonist or antagonist treatment), evidence-based psychosocial treatments, residential treatment, or combinations of these treatment options. Addiction treatment may be provided in outpatient or inpatient settings. In isolation, withdrawal management, harm-reduction services, low-barrier housing, and unstructured peer-based support would not be considered "addiction treatment".

Cultural safety and humility: Cultural safety can be understood as an outcome in which people feel safe when receiving care in an environment free from racism and discrimination. It results from respectful engagement that seeks to address power imbalances that are inherent in the healthcare system. Cultural humility is a process undertaken to understand, through self-reflection, personal and systemic biases and to develop and maintain respectful processes and relationships based on mutual trust; it requires humbly acknowledging oneself as a learner when attempting to understand another person's experience.[dd]

Diversion: Any non-intended or non-medical use of a prescribed opioid (including prescribed opioid agonist medication), or use by any individual other than the individual for whom it was prescribed.

Harm reduction: Policies and programs that aim to minimize immediate health, social, and economic harms (e.g., transmission of infectious disease, overdose mortality, criminal activity) associated with the use of psychoactive substances, without necessarily requiring a decrease in substance use or a goal of abstinence. Examples include needle and syringe exchange programs, take-home naloxone programs, supervised injection or consumption services, and outreach and education programs for high-risk populations.

Health care provider: A trained and qualified health care provider empowered to provide care related to iOAT, including supervision of medication administration and, in some jurisdictions and models of care, health care provider administered intramuscular or subcutaneous injection. May refer to doctors, nurse practitioners, Registered Nurses, Registered Psychiatric Nurses, Licensed Practical Nurses, and pharmacists.

2SLGBTQ+: Two-Spirit, lesbian, gay, bisexual, trans, queer, and other gender and sexually diverse individuals.

dd Definitions borrowed and lightly adapted from the First Nation's Health Authority.

Two-Spirit: A term used by some North American Indigenous societies to describe people with diverse gender identities, gender expressions, gender roles, and sexual orientations. Dual-gendered, or 'two-spirited' people have been and are viewed differently in different Indigenous communities.[ee]

Lesbian: A woman whose enduring physical, romantic, and/or emotional attraction is to other women. Some lesbians may prefer to identify as gay (adj.) or as gay women.[ff]

Gay: The adjective used to describe people whose enduring physical, romantic, and/or emotional attractions are to people of the same gender.[ff]

Bisexual: A person who has the capacity to form enduring physical, romantic, and/or emotional attractions to those of the same gender and those of another gender. People may experience this attraction in differing ways and degrees over their lifetime.[ff]

Trans: Trans is an umbrella term that describes a wide range of people whose gender and/or gender expression differ from their assigned sex and/or the societal and cultural expectations of their assigned sex.[ff]

Queer: An adjective used by some people, particularly younger people, whose sexuality is not heterosexual. Once considered a pejorative term, queer has been reclaimed by some 2SLGBTQ+ people to describe themselves; however, it is not a universally accepted term even within the 2SLGBTQ+ community.[ff]

Medical management: Medical management for opioid use disorder is medically focused, unstructured, informal counselling provided by the treating clinician in conjunction with pharmacological treatment. Medical management includes but is not limited to, performing health and wellness checks, providing support and advice, assessing motivation and identifying barriers to change, creating a treatment plan, fostering medication adherence, optimizing dosing, supporting treatment adherence and relapse prevention, and providing referrals to appropriate health and social services.

Mutual-support/peer-support programs: Support that is provided through a network of peers through meetings, open discussions of personal experiences and barriers to asking for help, sponsorship, 12-step programs, and other tools of recovery. Examples include Alcoholics Anonymous, Narcotics Anonymous, SMART Recovery, and LifeRing Secular Recovery.

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ee Definition borrowed and lightly adapted from Qmunity's "Queer Terminology from A to Q"

ff Definitions borrowed and lightly adapted from GLAAD Media Reference Guide

Opioid agonist: Any substance that binds to and activates mu (μ) opioid receptors, providing relief from withdrawal symptoms and cravings in people with opioid use disorder, and pain relief if used for chronic pain management. Oral opioid agonists used for treating opioid use disorder include methadone, buprenorphine, and slow-release oral morphine. Injectable opioid agonists used for treating opioid use disorder include diacetylmorphine and hydromorphone.

Opioid agonist treatment (OAT): Opioid agonist medications prescribed for the treatment of opioid use disorder. Opioid agonist treatment is typically provided in conjunction with provider-led counselling; long-term substance-use monitoring (e.g., regular assessment, follow-up, and urine drug tests); comprehensive preventive and primary care; and referrals to psychosocial treatment interventions, psychosocial supports, and specialist care as required. In this document, OAT refers to long-term (>6 months) treatment with an opioid agonist medication that has an evidence base for use in the treatment of opioid use disorder. "Opioid agonist treatment (OAT)" is the preferred terminology, representing an intentional shift from the use of “opioid substitution treatment (OST)”, “opioid maintenance treatment (OMT)”, and “opioid replacement therapy (ORT)”.

Buprenorphine: A long-acting synthetic opioid that acts as a partial mu (μ) opioid receptor agonist with a half-life of approximately 24 to 42 hours. Buprenorphine has a high affinity for the opioid receptor, but as a partial agonist has a lower intrinsic activity or effect at the opioid receptor compared to full agonist opioids. These pharmacological properties create a "ceiling” on opioidergic effects—including respiratory depression—at higher doses. Buprenorphine's high affinity for the opioid receptor also confers an antagonistic effect on other opioids; it preferentially binds to the receptor and displaces other opioids if they are present, which can cause precipitated withdrawal (see below). In Canada, buprenorphine is available in a combined formulation with naloxone (see below). Buprenorphine implant and depot injections were recently approved by Health Canada, but have not yet been added to provincial formularies.

Buprenorphine/naloxone: A 4:1 combined formulation of buprenorphine and naloxone, available as a sublingual tablet in Canada. Naloxone is an opioid antagonist with poor oral bioavailability when swallowed or administered sublingually, and is included to deter non-medical injection and insufflation. When buprenorphine/naloxone is taken as directed sublingually, the naloxone component has negligible effects and the therapeutic effect of buprenorphine predominates. However, if diverted for use via insufflation, subcutaneous, intramuscular, or intravenous routes, sufficient naloxone is absorbed to induce some withdrawal symptoms in physically dependent active opioid users. Buprenorphine/naloxone is generally taken once daily, but due to its favourable safety profile and pharmacological properties, it can also be prescribed at higher doses on alternate-day schedules.

Diacetylmorphine: A short-acting, semi-synthetic opioid, diacetylmorphine has a rapid onset of action and a short half-life. Injected diacetylmorphine avoids first-pass metabolism and crosses rapidly into the brain where it is deacetylated into an inactive 3-monoacetylmorphine and an active 6-monoacetylmorphine which is then deacetylated into morphine, which acts as a full mu (μ) opioid receptor agonist. Injectable diacetylmorphine is used as a treatment for severe opioid use disorder in Canada and several European jurisdictions.

Hydromorphone: A short-acting, semi-synthetic mu (μ) opioid receptor agonist. Due to regulatory barriers limiting access to diacetylmorphine, hydromorphone was studied as an alternative to diacetylmorphine for the treatment of severe opioid use disorder and found to be non-inferior.

Methadone: A long-acting synthetic opioid that acts as a full mu (μ) opioid receptor agonist. It has a half-life of approximately 24 to 36 hours and is well absorbed. In Canada, it is most frequently administered as an oral solution, generally given as a single daily dose. Methadone tablets are also available in a limited context (e.g., for travel) in some jurisdictions.

Slow-release oral morphine: A 24-hour slow-release formulation of morphine, a full agonist at the mu (μ) opioid receptor, that is taken orally once per day. In Canada, slow-release oral morphine is available as a capsule containing polymer-coated pellets (to slow absorption and release) of morphine sulfate. Its elimination half-life is approximately 11 to 13 hours. It is currently approved for pain management in Canada, and its use for treatment of opioid use disorder would be considered off-label.

Opioid antagonist: Medication that works by blocking opioid receptors, preventing the body from responding to opioids. Opioid antagonist medications may be used to rapidly displace opioid agonist molecules from receptors in an overdose situation (e.g., naloxone), or to facilitate continued abstinence from using opioid drugs (e.g., naltrexone). In Canada, naloxone is available in an intramuscular injection or intranasal spray (depending on availability), while naltrexone is available as an oral tablet taken once per day.

Opioid use disorder (OUD): A problematic pattern of opioid use leading to clinically significant impairment or distress that meets the DSM-5 Diagnostic Criteria for Opioid Use Disorder (see Appendix 4). Opioid use disorder includes the use of synthetic and/or naturally derived opioids, whether prescribed or illegally obtained. The DSM-5 terminology represents a deliberate shift away from DSM-IV terminology of “opioid abuse” or “opioid dependence”, which may be considered pejorative and/or stigmatizing, to describe this condition.

Psychosocial supports: Non-therapeutic social support services that aim to improve overall individual and/or family stability and quality of life, which may include community services, social and family services, temporary and supported housing, income-assistance programs, vocational training, life-skills education, and legal services.

Psychosocial treatment interventions: Structured and/or manualized treatments delivered by a trained care provider that incorporate principles of cognitive behavioural therapy, interpersonal therapy, motivational interviewing, dialectical behaviour therapy, contingency management, structured relapse prevention, biofeedback, family and/or group counselling. Psychosocial interventions may include culturally specific approaches such as traditional healers, elder involvement, and Indigenous healing ceremonies.

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

Relapse: May be defined differently by each person, however, a general definition would include a re-emergence of or increase in severity of opioid use disorder symptoms and/or harms related to opioid use following a period of stability.

Stabilization: Stabilization will be patient-specific, depending on each patient's circumstances and needs and how they change over time. Patients' DSM-5 diagnoses, physical and mental health comorbidities, and social determinants of health (e.g., poverty, homelessness) should be identified at baseline and tracked over time. Stabilization includes clinical stabilization (e.g., lack of cravings, improved sleep quality and duration, and overall wellbeing) as well as psychosocial stabilization (e.g., integrating new activities, re-connecting with family, and attaining safe housing).

Trauma: Trauma can be understood as an experience that overwhelms an individual's capacity to cope. Trauma can result from a series of events or one significant event. Trauma may occur in early life (e.g., child abuse, disrupted attachment, witnessing others experience violence, or neglect) or later in life (e.g., accidents, war, unexpected loss, violence, or other life events out of one's control). Trauma can be devastating and can interfere with a person's sense of safety, sense of self, and sense of self-efficacy. Trauma can also impact a person's ability to regulate emotions and navigate relationships. People who have experienced trauma may use substances or other behaviours to cope with feelings of shame, terror, and powerlessness.

> **Intergenerational trauma:** The transmission of historical oppression and unresolved trauma from caregivers to children. The concept of intergenerational or historical trauma was developed by Indigenous peoples in Canada in the 1980s to explain the cycle of trauma they were seeing in their communities due to the residential school system, loss of culture, and colonization more broadly. May also be used to describe the emotional effects, adaptations, and coping patterns developed when living with a trauma survivor.

gg Borrowed from the Substance Abuse and Mental Health Administration's "SAMHSA's Working Definition of Recovery: 10 Guiding Principles of Recovery"

Trauma-informed practice: Health care and other services grounded in an understanding of trauma that integrate the following principles: trauma awareness; safety and trustworthiness; choice, collaboration, and connection; strengths-based approaches, and skill-building. Trauma-informed services prioritize safety and empowerment and avoid approaches that are confrontational.

Treatment refractory: Refers to opioid use disorder which has been treated with standard first-line pharmacological treatments, with the individual experiencing insufficient benefit and/or continuing to use illicit opioids and experiencing poor physical and mental health as well as poor social integration. It should be noted that there has been an intentional shift away from the use of "treatment refractory," as it may inadvertently perpetuate stigma against individuals with opioid use disorder. This document uses this term, when necessary, to reflect its use in the scientific literature. However, substance use disorders are known to be chronic, relapsing conditions which may require multiple treatment approaches across the lifespan, thus rendering such a term and concept otherwise moot.

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