Title: Study to Assess Longer-term Opioid Medication Effectiveness (SALOME)

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1.0 Protocol summary

Title and Study Number

Study to Assess Longer-term Opioid Medication Effectiveness (SALOME)

Phase

III

Objectives and Variables

Primary:

- Injectable hydromorphone is not inferior to injectable diacetylmorphine in reducing illicit heroin use in chronic injection opioid users after six months of treatment (Stage I).

- Following at least six-months of treatment with injection opioids, a switch to the oral form of the medications is not inferior to continued injection treatment over the following six-months (Stage II).

Secondary:

Secondary outcomes will be evaluated looking at the benefits for the drug users and society of each form of treatment including health status, treatment retention, use of additional methadone, cocaine use and criminal involvement.

Design

This is a two-stage phase III, single site (Vancouver), randomized, double blind controlled trial involving a total of 202 individuals with chronic opioid-dependence who are not benefiting currently from conventional therapies.

Stage I: Half of the 202 participants will be randomized to receive injectable diacetylmorphine, and the other half will receive injectable hydromorphone. Stage I will involve 6-months of treatment and the primary outcome will be change in illicit heroin use in the prior 30 days at 6 months.

Stage II: All volunteers retained in injection treatment at the end of Stage I will be eligible to enter Stage II. Half the participants will then be randomized to continue injection treatment exactly as in Stage I on a blinded basis while the other half will switch to the oral equivalent of the same medication (diacetylmorphine or hydromorphone). Stage II will involve 6-months of treatment and the primary outcome will be illicit heroin use in the prior 30 days at 6 months after randomization into Stage II.

Participants

A total of 202 participants will be recruited. Men and women over the age of 19, chronic, opioid-dependent, daily opioid injection drug users who are currently injecting and who have previously attempted methadone maintenance treatment.
Treatment

Stage I: Fifty percent of the participants (101) will be randomized to receive injected diacetylmorphine and 50% (101) will be randomized to injected hydromorphone. Participants will self-inject the medications.

Stage II: Half the volunteers retained at the end of Stage I will be randomized to continue injection treatment or to switch to the oral equivalent of the same medication. Thus 50% of those randomized to injected diacetylmorphine will continue with injected diacetylmorphine, the other 50% will switch to oral diacetylmorphine. In the hydromorphone group, 50% will continue with injected hydromorphone and the other 50% will switch to oral hydromorphone.

Duration

The expected study duration is 24 months for the participants. The first 6 months (Stage I) is active treatment with either injected diacetylmorphine or hydromorphone, the next 6 months (stage II) is either oral or injected diacetylmorphine or hydromorphone. The second year is for follow up including weaning from diacetylmorphine or hydromorphone, switch to available treatment.

Sample Size and Power Calculations

Sample size requirements for the study were calculated based on illicit heroin use as the primary outcome. For stage I, a non-inferiority trial with an expected decline of 20 days with a SD = 11.0 (data derived from the NAOMI results) from baseline, a margin of 4 days, a power of 0.90, an expected loss-to-follow-up rate of 0.05 and a one-sided alpha level of 0.05, requires 202 subjects (101 per group). The confidence intervals were calculated based on normal approximation.

It is possible that the data for the primary outcome will not be normally distributed. If we use the binary outcome (decline to ≤ 3 days of illicit heroin use) defined as success, we can expect a success rate of 0.80 based on existing data. The margin of 4 days translates to a relative effect size of 0.80. For stage I, a non-inferiority trial with an expected success rate of 0.80, a lower margin set at 0.80 relative to expected, a power of 0.90, an expected loss-to-follow-up rate of 0.05 and a one-sided alpha level of 0.05, requires 194 subjects (97 per group). We can therefore safely utilize a sample size of 202.

With a sample size of N = 202, we can expect that approximately 172 participants will enter into phase II. Under the same assumptions as above, this will yield a non-inferiority trial with power = 0.86.
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2.0 Ethics

2.1. Ethical conduct of the study

This study will be conducted following ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Good Clinical Practice Guidelines\(^1\) and in Accordance with the Declaration of Helsinki\(^2\).

The study has received approval from the University of British Columbia and Providence Health Care (Vancouver) review ethics boards (REB). The conduct of the study and all amendments to the protocol will be reviewed by the Data Safety and Monitory Board (DSMB). Amendments to the protocol will be submitted for approval by the REB.

Study medications require a Clinical Trial Application (CTA). The Therapeutic Products Directorate (TPD) of Health Canada notified us on October 6, 2009 that the 30 day time limit after receipt of a complete submission within which the Minister might object to the sale or importation of the study drugs pursuant to section C.05.006 of the Food and Drug Regulations (FDR) has expired. This means that the sale and importation of the study drugs for use in the clinical trial are authorized pursuant to section C.05.006 of the FDR. We have submitted several amendments to our initial CTA since then, and we have received No Objection Letter (NOL) in each occasion. In September 2, 2010, the TPD had no objection (see appendix – NOL Liquid form) to the amendment made to our CTA (a change in the oral formulations presentation, from capsules to liquid). We have received a NOL for the CTA-A (amendment) to manufacture hydromorphone from active pharmaceutical ingredient (compounding), and to prepare the oral solutions. We have also received an acknowledgment of our CTA-N (notification) for the stability test results for the oral solutions.

In June 2011 we obtained a Section 56 Exemption for using controlled narcotics in the SALOME study, from the Office of Controlled Substances (OCS). This exemption is valid for a year, and has been renewed each year until November 2014.

The study pharmacy operates under a license, granted by the Licences and Permits Division of the OCS. This license is valid for a year, and has been renewed until December 2014.

2.2. Participant information and consent

All participants will receive clear information about the study and will provide informed consent prior to any study procedures being performed. The informed consent will be obtained at the first screening appointment. For additional information on health status, research staff will obtain participants' consent to request health records and consult with their current other health care providers. This also includes permission to track participants who drop out of the treatment component.

3.0 Number of Centres

The study is designed as a single-centre randomized controlled trial of 202 treatment refractory injection opioid users involving participants in Vancouver.
4.0 Trial management

The SALOME study will be conducted in two separate facilities: a treatment clinic and a research centre that operate independently. The research centre will handle trial recruitment and screening, baseline assessments, and ensure research follow-up through each of the follow-up assessments. Data collected by the research centre will not be shared with the treatment clinic and will not affect the clinical care received by the study participant. The data collected will be managed at the site level as well as at the trial level using a uniform set of guidelines and procedures. The functions of the trial steering committee will be undertaken by the Trial Management Committee:

Trial steering committee

The overall management of the trial will be overseen by a Steering Committee, providing overall supervision of the trial and ensuring that it is being conducted in accordance with the principles of GCP and the relevant regulations. The SALOME Steering Committee is comprised of the Principal Investigators, the study pharmacist (License Dealer for the study), the Clinical Lead, the Operations Leader HIV/AIDS & Addiction Services, the Vice President of Clinical Programs & Chief of Professional Practice and the Director of Communications & Public Affairs. The Steering Committee oversees the day-to-day management of the trial, resolving questions about eligibility, enrolment, randomization, drug dosing, transition and weaning, grading and disposition of adverse events, determination of endpoint questions that need resolution, as well as managing site specific operational issues and liaising with funders and other stakeholders and community advisory committees.

Data safety and monitoring committee.

SALOME’s independent Data Safety and Monitoring Board (DSMB) is composed of experts in the fields of addiction medicine, clinical trial methodology and ethics (David Roy, Janet Raboud, Michael Lester, Carl Hart). The DSMB will review the accruing trial data and assess whether there are any safety issues that should be brought to participants’ attention or any reasons for the trial not to continue. Interim monitoring reports to the DSMB focus on participant intake, retention within each treatment modality and the trial at large, baseline assessment of study participants and monitoring of adverse events and severe adverse events witnessed in the clinical treatment sites. In addition, efficacy and safety are assessed as part of the interim monitoring.

5.0 List of Investigators

The study involves a number of investigators from the following study site: St. Paul’s Hospital, 588B–1081 Burrard St., Vancouver, B.C., V6Z 1Y6

Dr. Eugenia Oviedo-Joekes (Principal Investigator), School of Population and Public Health, University of British Columbia. Centre for Health Evaluation & Outcome Sciences, Providence Health Care
Role of each principal investigators and co-investigators

The SALOME trial will be led by two Principal Investigators, Dr. E. Oviedo-Joekes (PhD, Psychologist) and Dr. M. Krausz (PhD, MD). Both PIs have extensive experience in trials with injectable medication; they will contribute substantially to the objectives of this study and will be responsible for its evaluation. As the Providence Health Care BC Leadership Chair in Addiction Research, Dr. Krausz has significant expertise in clinical research and treatment of mental illness and addiction. Dr. Krausz is the qualified investigator and is responsible for the conduct of the clinical study. Dr. M. Krausz is in charge of the supervision of the service and treatment provision in the clinic, working with physicians and nurses, ensuring best practices and high quality of care. Dr. Oviedo-Joekes, Assistant Professor at the School of Population and Public Health (SPPH), at UBC, contributes with her expertise in psychology, behavioural sciences methodology and treatment evaluation; she is also part of the NAOMI (North American Opiate Medication Initiative) study. Dr. Oviedo-Joekes leads the research team, trains the research staff, meets with the community advisory board, supervises recruitment, randomization and enrolment of participants in the study, ensures the quality of data collection, evaluates progress of the project, and oversees the work of the Clinical Trial Coordinator. She also leads our dialogues with Health Canada to obtain the required permits and works closely with the study pharmacist and co-Investigator (Co-I), Amin Janmohamed, on the manufacturing and testing procedures of the study medications.

Co-I, Dr. Schechter is Professor and Head of the School of Population and Public Health at UBC. He will collaborate with his expertise as a clinical epidemiologist and as the PI of the NAOMI trial. Co-I, Dr Brissette, also part of the NAOMI team, is the Medical Monitor. She contributes with her clinical expertise to review adverse events and other clinical consultations. Dr. Bruneau brings her clinical research expertise and highly valued epidemiological support. Dr. Schütz is a highly experienced clinical investigator, bringing his expertise as a social psychiatrist. Dr. Anis and Dr. Bansback bring their expertise on Health Economics and Pharmacoeconomics and Cost Effectiveness, and will prepare the health economics analysis of this study. Amin Janmohamed is the study pharmacist; he provides his expertise and experience as the study pharmacist for the NAOMI study and the clinic site pharmacy director; he is also the authorized Licensed Dealer for the study, by Health Canada.
6.0 Justification

Opioid dependence, most commonly manifested as heroin dependence, is a chronic, relapsing condition estimated to affect more than one million individuals in North America. The personal risks include fatal overdoses, infections including endocarditis, HIV and hepatitis C, social disintegration, violence and crime. The burdens on communities include medical care, public health and criminal justice costs as well as public disorder and crimes against people and property.

Overall abstinence-based therapies have shown low effectiveness, with less than a 30% response rate after one year. This has led to the need for opioid substitution-based therapies. Methadone is a synthetic opioid that binds to opioid receptors thus reducing the craving and withdrawal symptoms that perpetuate opioid use. Methadone has a half-life of 15 to 60 hours, and its bioavailability is almost the same whether administered orally or injected, allowing for once-daily oral administration. Methadone Maintenance Treatment (MMT), in which opioid dependent individuals receive methadone orally once daily, is the most widely studied and effective treatment for opioid addiction and it has led to marked improvements in treatment.

Methadone, the gold standard substitution treatment, has been shown to be effective in reducing major risks associated with untreated opioid dependence in those participants who are attracted into and successfully retained in treatment. However, there is a subgroup of 15 to 25% of the most adversely affected chronic opioid dependent individuals who do not respond well to this treatment. Such individuals are either not retained in MMT for very long or continue to use illicit opioids while in treatment. For these participants studies in Europe and Canada (NAOMI, CIHR-funded North American Opiate Medication Initiative) have suggested that maintenance therapy with injected diacetylmorphine (DAM), the active ingredient in heroin, can be an effective adjunct treatment for such individuals. The hypothesis is that by providing medically prescribed pharmaceutical-grade heroin at prescribed dosages in sterile conditions within clinics staffed by doctors, nurses and counsellors, chronic treatment-refractory opioid-dependent individuals: (1) be better attracted into and retained in treatment; (2) be protected from harms such as overdose, HIV and hepatitis C infection; (3) be removed from destructive cycles of crime, prostitution, etc. that are often required to maintain heroin addiction; and (4) benefit from prolonged exposure to medical and psycho-social support services.

Opioid Dependence:

Opioid dependence, most commonly manifested as heroin dependence, is considered a chronic, relapsing disease. Opioids such as heroin activate opioid receptors in the brain (and the body), and this stimulation results in feelings of euphoria, triggering the pleasure circuit and releasing excess amounts of dopamine. Research suggests that this release of dopamine and the activation of the reward system can lead to substance dependence or addiction. Once physically dependent, individuals suffer severe withdrawal symptoms including nausea, vomiting, sweating, abdominal pain, and agitation if the drug is not taken. Injection drug use places users at risk of contracting HIV, Hepatitis C, and other blood-borne pathogens. Co-morbid mental illness, cardio-pulmonary conditions and serious bacterial infections are also common in populations with opioid dependence, and the possibility of overdose leads to greatly elevated mortality risk. Chronic opioid dependence is also associated with poor psychosocial functioning, given that it is generally accompanied by unemployment, imprisonment, poor housing conditions, and illegal activities.

Opioid Addiction Treatment
Strategies to treat and stabilize the problems associated with illicit opioid use are many and varied. Treatment ranges from abstinence (with or without medications) to substitution treatment, with or without concomitant psychosocial support or psychiatric therapy. Recent reviews suggest that substitution treatment is the most effective approach\textsuperscript{25, 26}. In Western Countries methadone is the most widely used opioid agonist in substitution treatment. Other alternatives are currently available depending on the country: buprenorphine\textsuperscript{27}, morphine\textsuperscript{28, 29}, dihydrocodeine \textsuperscript{30, 31} and diacetylmorphine \textsuperscript{32} among others. An alternative oral opioid substitution therapy, levo-alpha acetylmethadol (LAAM), was approved in 1993 for use in some countries though never in Canada; however following case reports of life-threatening cardiac rhythm disorders \textsuperscript{33} in the United States and Europe it is no longer available.

\textit{Methadone Maintenance Therapy (MMT)}

Methadone is a long-acting synthetic opioid agonist that is easily absorbed when taken orally and has a half-life of approximately 25 hours, allowing once daily administration. MMT provides methadone orally on a regular (usually daily) basis to the patient \textsuperscript{7}. Studies have suggested methadone is successful in blocking the effects of opioid withdrawal symptoms\textsuperscript{34}. MMT is effective in reducing major risks, harms and costs associated with untreated opioid dependence with patients attracted into and successfully retained in methadone treatment \textsuperscript{10}. Best treatment outcomes have generally been correlated with a number of program factors, including high level and quality of psycho-social care services, duration of treatment retention, sufficient methadone dosing, and a basic level of patient identification with program rules and staff\textsuperscript{34-36}.

However, MMT is not always successful at retaining patients in treatment for prolonged periods. For example, in British Columbia only 52\% of MMT patients are retained for at least a year \textsuperscript{37} in line with estimates of retention found in a National Institute of Drug Abuse review\textsuperscript{38}. Other programs show higher retention rates, between 60 and 80\%, such as in Ontario \textsuperscript{39}, in a low-threshold program in Montreal\textsuperscript{40}, and in most of the European Countries\textsuperscript{41, 42}. A variety of reasons for patients not being successfully maintained in MMT have been documented. The most important reason is likely the lack of adherence to best practices and clinical guidelines in prescribing MMT, with many patients receiving less than the minimum effective maintenance dose of 60 mg per day\textsuperscript{43}. Other reasons include difficulties with side effects such as nausea, numbness, severe withdrawal, and depression, and the desire for engagement in the social rituals and networks of injection drug use, including the use of needles, ‘scoring’, or the contacts with the sub-culture and its environment\textsuperscript{44, 45}. Therefore, while conventional pharmacotherapies have proven effective for some individuals, alternative treatment modalities are needed for opioid addicts who cannot be attracted into or productively retained in conventional forms of opioid addiction treatment.

\textit{Heroin-Assisted Treatment (HAT)}

Diacetylmorphine (DAM) is the active opioid found in illicit “street” heroin and can be manufactured as a pure pharmaceutical product. In light of the sub-optimal success of conventional treatments, several countries have recently begun to provide diacetylmorphine to treatment-resistant opioid users as an alternative treatment modality. Where available, DAM is provided in clinics where patients receive prescribed doses that are self-injected under the supervision of health care staff.

Several randomized trials and cohort studies have shown that heroin assisted treatment – provided in specialized clinics -- is feasible, safe and effective when treating long-term chronic injecting opioid users for whom the available treatments are not effective\textsuperscript{14-17, 19}. Patients treated with DAM improved
in a number of dimensions, including reduction of illicit heroin and cocaine use, decreased criminal activity, and improvements in physical and mental health.

HAT is not simply a pharmacotherapy. It is a treatment approach that is situated within a context involving neighbourhood factors, the local drug scene, housing, policing, medical care and other treatment services. NAOMI was designed to investigate the effectiveness of HAT in the North American context, i.e. at several Canadian and USA cities. In the end, however, the study could only be conducted in Canada.

The NAOMI study

NAOMI was a parallel, open-label, phase III randomized controlled trial (n=251) conducted in Vancouver and Montreal between March 2005 and July 2008. Long-term heroin injectors who had not benefited from at least 2 previous treatment attempts were randomized to receive oral MMT (n=111) or injected diacetylmorphine (n=115) or injected hydromorphone (n=25). The injectable medications were dispensed in a double-blind basis. The DAM group could add or switch to methadone if desired. Primary outcomes were: (1) Retention in addiction treatment or drug-free status at 12 months; (2) clinical response at 12 months based on the European version of the Addiction Severity Index (ASI)46.

The primary outcomes were determined for 95% of participants. Based on intention-to treat analysis, the rates of retention in addiction treatment in the DAM and MMT groups were 87.8% and 54.1% (RR=1.62; CI 95%=1.35-1.95; p<0.001). The clinical response rates were 67.0% vs. 47.8% respectively (RR= 1.40; 95% CI= 1.11-1.77; p=0.004)17.

The NAOMI study results are consistent with European results that suggest greater effectiveness of DAM compared to MMT in chronic, treatment-refractory opioid users. Injected diacetylmorphine, administered under medical supervision, offered additional benefits over and above MMT alone for patients with opioid addiction who are refractory to treatment14-19.

Safety of diacetylmorphine

In the NAOMI study, overdoses and seizures were the two most common SAEs related to DAM and both were expected and have already been described as side effects of the pharmacological action of opioid medications47, 48. Particularly, seizure episodes have been already described in the literature as having a possible connection with the use of intravenous heroin49, 50. Nevertheless, seizures related to heroin use are commonly associated with the co-use of other substances, especially crack-cocaine48 and benzodiazepines14, as in the case of the NAOMI patients17.

Heroin is a respiratory depressant and, strictly speaking, heroin injection is less safe than oral treatments51, 52. Such considerations, however, should also take into account the relative safety of medically prescribed heroin compared with street opioids. When injected opioids are taken under the supervision of health care staff, overdoses and seizures have been shown to be effectively treated52 14-17, 19. In the NAOMI study, all drug overdoses and seizures at the clinics were easily controlled and resolved without sequelae or treatment discontinuation. Had these overdoses occurred under circumstances in which no medical help was immediately available, the outcomes may have been worse.

Hydromorphone

Studies have indicated that diacetylmorphine and hydromorphone, a licensed drug in North America, produce similar clinical and subjective effects, thus either drug may adequately substitute for the other53, 54. Hydromorphone is a potent semi-synthetic opioid analgesic widely used for the management of postoperative pain, and included in clinical practice guidelines for the management of
cancer-related pain\textsuperscript{55}. With an action profile to that of morphine, there is little difference between hydromorphone and other mu opioid receptor agonists in terms of analgesic efficacy or adverse effects\textsuperscript{56}. Moreover, its similarity with diacetylmorphine allows the use of hydromorphone as the ‘challenge’ drug in behavioural experimental studying heroin dependence\textsuperscript{57-59}.

Despite the potential role of hydromorphone, it has never been evaluated as a substitution treatment for opioid addiction. The design of the NAOMI study included a group where participants received either diacetylmorphine or hydromorphone, both injecting, in a double blind basis, for the purpose of validation of self-reported use of street heroin in urine. The evaluation of the double-blind showed that most participants in both groups thought they were definitely or possible receiving heroin. None of participants in the hydromorphone group thought they were definitely receiving this drug and 3 (12\%) thought that they were possible receiving it. Participants treated with diacetylmorphine and hydromorphone showed a significant decline in the Drug, and Legal composite scores of the EuropASI.

In this pilot evaluation, the response among those individuals randomized to receive hydromorphone did not show differences compared to those on diacetylmorphine in their illicit drug use, illegal activities, and physical and mental health. For example, retention and response rates for the HDM group were 88\% and 64\% respectively compared to 87.8\% and 67\% in the DAM group. Regarding the use of illicit heroin in the prior month, from baseline to the end of the study, it decreased from 26.6 to 5.3 days in the DAM group and from 26.3 to 5.2 days in the HDM group\textsuperscript{60}.

The NAOMI results suggest that hydromorphone may be equally effective as diacetylmorphine as opioid-agonist substitution treatment in this severely affected subgroup of participants. However, as this was not anticipated, the NAOMI trial was not powered to study this question definitively. If non-inferiority of HDM were to be confirmed, the potential availability of this type of treatment around the world would expand dramatically. The findings in the NAOMI study may provide a critically important alternative way to address this since hydromorphone is a licensed, synthetic opioid medication widely used in pain treatment that carries far less stigma than heroin.

\textit{SALOME (Study to Assess Long-term Opioid Maintenance Effectiveness)}

Regardless of the effectiveness of DAM, there is much stigma attached to the use of ‘heroin’, even when medically prescribed, which may limit its uptake in many countries. The above mentioned finding in the NAOMI study in relation to hydromorphone (no breaking of the blinding, similar response compared to DAM) may provide a critically important way to address this. Therefore, in Stage I of SALOME, we propose to test (on a double-blind basis) whether hydromorphone effectiveness is a non-inferior alternative to diacetylmorphine in the treatment of chronic, multi-morbid opioid-dependent individuals who have not benefited sufficient from conventional treatments. This is the first question to be addressed in the proposed study.

The second question addresses route of administration. It is clear that the intravenous administration of medically prescribed opioid treatment, whether DAM or HDM, places a number of burdens on both the patient and the health care system. Opioid injection as a substitution treatment is a challenging form of application in terms of the required clinical team, side effects associated with the drug and the route, and logistical physical and security requirements. Results from the Swiss HAT cohort show that after a period of stabilization involving injectable heroin (DAM), a significant number of patients switched to oral DAM tablets (totally or combined with injected DAM)\textsuperscript{61,62}. In Stage II of SALOME, we will randomize participants completing Stage I (that is, injection DAM vs. injection HDM) to either continue the injection drug or switch to its oral equivalent. This phase will allow a test of the potential value of switching patients to a much less risky and more convenient route of administration following
stabilization with injection medication. If non-inferiority is shown in both stages, we will have established that the more widely acceptable drug, hydromorphone, can be used to stabilize the most adversely affected cases of chronic opioid dependence in a medically prescribed injection program, and that these individuals, once stabilized, can safely be switched to the safer, more convenient and more feasible oral route of administration.

**Pharmacological and subjective effects of diacetylmorphine compared to hydromorphone**

Lab studies comparing hydromorphone and diacetylmorphine:

The pharmacological effects of hydromorphone compared to diacetylmorphine were tested in one study carried out by B. Brands, D. C. Marsh, et al. from the Centre for Addiction and Mental Health, Toronto (Canada) and G. E. Bigelow, et al. from the Johns Hopkins University School of Medicine (United States)\(^{53, 63}\). Eighteen individuals participated in the study, non-daily intravenous opioid abusers, not physically dependent, with a mean age of 37. Lifetime average use of illicit heroin was 5 years and currently, 7 days in the prior month. The experimental sessions were conducted in residential human laboratory facilities. The design of the study included a placebo and 3 active dose levels of intravenous and subcutaneous diacetylmorphine and hydromorphone, evaluated in a cross-over design utilizing double-blind, within-subject, double-dummy, randomized procedures. Three variables were manipulated: (1) Drug: diacetylmorphine vs. hydromorphone, (2) Dose: varied over a 4-fold range, and (3) Route of Administration: intravenous vs. subcutaneous. Hydromorphone was assumed to be four times more potent than diacetylmorphine. Thus, 16 test conditions were studied: diacetylmorphine intravenously at 0, 2.5, 5, and 10 mg, hydromorphone intravenously at 0, 0.63, 1.25 and 2.5 mg, diacetylmorphine subcutaneously at 0, 5, 10 and 20 mg and hydromorphone subcutaneously at 0, 1.25, 2.5 and 5 mg.

Physiological, subjective, behavioural and psychomotor measures were conducted before, and for 3 hrs after active drug or placebo administration. Results demonstrated that diacetylmorphine and hydromorphone produced similar effects, had similar time courses, peak effect times, onsets of action, and approximately parallel dose-response curves on most measures. However, participants’ answers in the intravenous diacetylmorphine and hydromorphone group were different when asked if they were receiving ‘heroin’: there were 23 affirmative responses among those receiving diacetylmorphine vs. 7 among those receiving hydromorphone. No differences were found among those receiving the drugs subcutaneously (28 vs. 22). The authors concluded that hydromorphone and diacetylmorphine might be pharmacologically indistinguishably but appeared subjectively distinguishable by the intravenous route.

Assessment of the success of the blinding in the NAOMI study:

In the NAOMI study, the assessment of the double-blind between diacetylmorphine and hydromorphone was conducted by asking participants, at the end of their treatment, which drug they thought they had received. Five options were offered: heroin definitely; heroin possibly, not sure; Dilaudid® possible; Dilaudid® definitely. The evaluation of the double-blind showed that most participants in both groups thought they were definitely or possibly receiving heroin. None of the participants in the hydromorphone group thought they were definitely receiving this drug and only 3 (12%) thought that they were possibly receiving it\(^60\). However, the blinding was not evaluated at the beginning of the study and did not include the evaluation by the health care providers.

It has been suggested that in double-blind trials, participants tend to think they have received the appealing treatment or drug choice if the treatment outcome is positive. Thus, the blinding evaluation
is not anymore about treatment administered, but about the treatment effectiveness. However, this was not the case in NAOMI. Among responders and non-responders, 44.8% and 53.7% of the participants thought they were definitively receiving diacetylmorphine, respectively. Retained and non-retained participants showed the same pattern (46.6% and 58.3%).

The safety profile of hydromorphone, compared to diacetylmorphine was similar. Also, 44.0% of the participants without a SAE and 54.5% of those with at least one SAE thought they were receiving definitely receiving diacetylmorphine, suggesting that the perception of side effects and adverse events did not lead to breaking of the blinding.

The assessment of the double-blind in the NAOMI study indicated that none of the people treated with hydromorphone thought they were definitely receiving this medication, indicating that a) the blinding was not broken and b) suggesting that participants can take hydromorphone for diacetylmorphine under a given context. Moreover, exploratory analysis of the impact of treatment efficacy and side effects showed no differences among those who where convinced they received the desired treatment (diacetylmorphine). These outcomes lead to the preliminary conclusion that the guessing of the blinding was not inducted by treatment effectiveness or side effects, a common misinterpretation when assessing double-blind.

The results regarding the success of the blinding in the NAOMI study dissent with those in the above described study: while in NAOMI participants do not seem to recognize if they received intravenous (mostly) diacetylmorphine or hydromorphone, participants in the lab study seems to do so. However, the design of these studies presents some key differences that can account for this disagreement in the results of participants’ evaluation of the blinding, summarized as follows:

a) Setting and nature of the study: Diacetylmorphine and hydromorphone in Brands and Bigelow’s study were dispensed in the context of a lab study, testing their pharmacological profiles. However in NAOMI (and so will be SALOME) participants received these medications as part of a randomized clinical trial testing efficacy of opioid maintenance treatments.

b) Participants: Participants’ profiles in these studies are very different. When NAOMI (and SALOME) was focused on long-term chronic opioid-dependent individuals, with daily use of illicit heroin in the prior month, Brands and Bigelow’s study participants were casual opioid-users.

c) Dosage: Since NAOMI was an opioid-maintenance treatment, the highest dose diacetylmorphine in Brands and Bigelow’s study (10 mg) was 40 times lower than the mean dose that participants received at NAOMI (mean daily dose 392.3 mg). This was also the case for hydromorphone (2.5 mg vs. 198 mg)

d) Route of administration: In Brands and Bigelow’s study intravenous and subcutaneous routes of administration were tested. In NAOMI, after more than 110,000 injections of hydromorphone and diacetylmorphine, there is no record of any participant using these drugs subcutaneously. In very few cases, when the vein system was too deteriorated to allow intravenous injections, participants administered themselves the drugs intramuscularly. Thus, the preliminary findings regarding subcutaneous administration of diacetylmorphine and hydromorphone would not be able to be studied in the context of the SALOME trial.

e) Conversion ratios between hydromorphone and diacetylmorphine: The conversion ratio hydromorphone to diacetylmorphine in Brands and Bigelow’s study was 1:4. NAOMI investigators hypothesized participants in that study may have been ‘unblinded’ due to lower doses of hydromorphone received in comparison with diacetylmorphine. For this reason, the NAOMI trial assumed a potency ratio of 1:3. However, the double-blind design plus the titration protocol
allowed each individual to reach their optimal dose for opioid-maintenance treatment, suggesting that a ratio closer to 1:2 might be more accurate\textsuperscript{69}.

f) Subjective distinction of hydromorphone: These two studies differ in the way the blinding was evaluated, to the point of considering comparisons with extreme caution. In the NAOMI study, the success of the blinding was evaluated by a researcher independent from the clinical team that asked the participants what drug they thought they received, giving them five choices (heroin/Dilaudid\textsuperscript{®}/definitively/possible/not sure). In Brands and Bigelow’s study participants were compelled to ‘guess’ the treatment (i.e. to discriminate the drug), monetary rewarding their correct answers. Participants were asked ‘Is this heroin?’ and received $8 for each correct “Yes” or “No” response, $2 for a “Can’t Tell” response and nothing for a wrong response. Training participants to discriminate drugs has different study aims than a clinical trial evaluating effectiveness, thus, comparing these two studies regarding the blinding evaluation will be unwise. Moreover, in a double-blind clinical trial if participants answer ‘don’t know’ in the blinding evaluation is a critical clue that they could not recognize the drugs but in Brands and Bigelow’s study that response option was discouraged.

The evidence on hydromorphone effectiveness, pharmacological and subjective effects compared to diacetylmorphine from Brands and Bigelow’s and NAOMI studies suggested that SALOME participants might take hydromorphone for diacetylmorphine. The evaluation and reporting of blinding in clinical trials is fundamental to presenting unbiased study results, and to make conclusions about the clinical effectiveness of a study drug\textsuperscript{64, 70}. The SALOME study will be to establish if participants can distinguish these drugs in the context of substitution treatment and the association between the success (or not) of the blinding with treatment effectiveness. In addition, the question if participants can take hydromorphone for diacetylmorphine is highly relevant to explore the possibility of providing open-label hydromorphone achieving similar results than when prescribed double-blinded with diacetylmorphine. This will provide a better understanding of the subjective drug effect of hydromorphone and diacetylmorphine in the context of medically supervised opioid-injection treatment.

7.0 Study Objectives

The general objectives of this study are to determine whether 1) the closely supervised provision of injectable, hydromorphone is as effective as injectable diacetylmorphine in recruiting, retaining, and benefiting chronic, multi-morbid opioid-dependent individuals who are currently not benefiting from conventional treatments, and 2) if the switch to the oral equivalent of hydromorphone and diacetylmorphine after six-months is as effective as the injection form.

\textit{Primary Hypotheses:}

A. Is injectable hydromorphone not inferior to injectable diacetylmorphine in reducing illicit heroin use in chronic injection opioid users after six months of treatment? (Stage I)

B. Following at least six-months of treatment with injection opioids, is a switch to the oral form of the medication not inferior to continued injection treatment over the following six-months? (Stage II).
8.0 Investigational Plan

8.1. Design

This is a two-stage single-site (Vancouver) phase III, randomized, double blind controlled trial involving a total of 202 individuals with chronic opioid-dependence who are not benefiting currently from conventional therapies (see Figure 1).

Stage I: Half of the 202 participants will be randomized to receive injectable diacetylmorphine, and the other half will receive injectable hydromorphone. This drug administration protocol is as per the NAOMI study and the medications will be provided on a double-blind basis with only study pharmacists aware of treatment allocation. Stage I will involve 6-months of treatment and the primary outcome will be illicit heroin use in the prior 30 days at 6 months.

Stage II: All volunteers retained in injection treatment at the end of Stage I will be eligible to enter Stage II (based on observed NAOMI data at 6-months, it is expected that 85% will enter the second Stage). Half the participants will then be randomized to continue injection treatment exactly as in Stage I on a blinded basis while the other half will switch to the oral equivalent of the same medication (DAM or HDM). Route of administration will not be blinded but the oral formulations will be given in a double blind basis. Stage II will involve 6-months of treatment and the primary outcome will be illicit heroin use in the prior 30 days at 6 months after randomization into Stage II.

Stage I (6-months)
Treatment A: injected diacetylmorphine
Treatment B: injected hydromorphone
Analysis: A vs. B

Stage II (6-months)
Treatment A1: continued injected diacetylmorphine
Treatment A2: switch to oral diacetylmorphine
Treatment B1: continued injected hydromorphone
Treatment B2: switch to oral hydromorphone

At any time during treatment, participants can, in consultation with and under the guidance of a study physician, add oral methadone to their treatment regimen. Participants can also at any time complete a full switch to oral methadone. However, participants no longer receiving either of the injection medications in Stage I will not be randomized into Stage II.
8.2. Randomization

To control for initial differences between treatment groups, randomization for Stage I will be stratified by gender (male and female; transgender individuals will be classified according to the gender they identify with). Randomization will be performed using a block randomization technique with variable block size using prepared tables at the Data Centre in St. Paul’s Hospital. The pharmacist will log into the system, where they will see participants' treatment assignment in order to prepare the drugs. Only the pharmacist will be able to log in to see treatment assignment. This will maintain the double-blind.

Randomization of eligible participants into Stage II will occur upon completion of Stage I so treatment assignment for Stage II will be unknown during Stage I. As shown in Figure 1, randomization into Stage II will be stratified based on Stage I allocation (diacetylmorphine and hydromorphone). It will be carried out as per Stage I, with the same randomization strata (gender). However, at this stage half of participants will switch to oral medications and the route of administration cannot be blinded. The research team will communicate via email to the pharmacy and the clinic coordinator that a participant has been randomized. The pharmacy will communicate to the Clinic Coordinator which route the participant is assigned and will prepare visually identical oral liquid in bottles to maintain the double-blind within the oral arm. In phase II, the clinic coordinator and physician will be responsible for
notifying the participants of the nature of the treatment that they will be receiving (continue on injectables or switch to oral).

8.3. Blinding

During Stage I, injected DAM and HDM will be delivered on a double blind basis. Identical coded multi-dose vials and pre-filled syringes of the injection drugs will be provided to the treatment clinic by the pharmacy. Pharmacologically equivalent doses of heroin and hydromorphone will be provided over a dose range, allowing blinded dose adjustment by treatment providers. This system was used and validated in the NAOMI trial and this blinding technique has proven to be effective.

For Stage II, it is impossible to blind oral vs. injection route of administration (oral medication plus injectable placebo vs. injected medication plus oral placebo) because placebo injection would be immediately recognized due to lack of the “rush” that occurs immediately upon active injection. Moreover, even if blinding were possible, our intent is to evaluate relative effectiveness including participants’ acceptance of being switched to the oral route. However, even though the participants know the route of administration, they will continue to be unaware of the medication they are receiving, DAM or HDM, until the end of the trial.

A range of pharmacologically equivalent doses of oral DAM and HDM will be provided, allowing for blinded dose adjustment.

There are data to assure that switching to oral administration will not unmask the drug treatment due to different bioavailability between oral heroin and oral hydromorphone. Peak plasma levels of HDM and DAM both occur at 30 to 60 minutes following oral administration. As previously noted, both drugs are blindly titrated by physicians (on the basis of DAM equivalents) to achieve a similar clinical effect. In addition, data from NAOMI show there was no unblinding of the injection drugs based on differential clinical effects. For all these reasons, we are confident that the oral administration arm will not become unblinded as to HDM vs. DAM.

It can be suggested that successful maintenance in phase I might bias the success in phase II. However, the question of switching from successful intravenous maintenance to oral maintenance is only clinically relevant to those who have been successfully maintained.

8.4. Transition and Weaning

At the end of the full study period (12-months, stages I and II combined) we are committed to helping all participants to transition to the best treatment available in the community that they will accept. The 12-month treatment period and 1-month transition period will be clearly explained in the consent. The transition period is mandated because the tested drugs are not licensed for addiction treatment outside the context of the trial. This transition protocol is similar as that followed in the NAOMI study.

9.0 Study Population
The study population is defined as chronic, opioid-dependent, injection drug users who are currently injecting and who have attempted at least 1 previous episode of opioid maintenance treatment.

9.1. Inclusion Criteria

To be eligible for Stage I of the study, participants must fulfill the following entry criteria:

a. Opioid Dependence as confirmed by DSM IV diagnostic criteria;

b. 19 years of age or older;

c. Resident of the greater metropolitan area (Vancouver);

d. At least 5 years of opioid use;

e. Poor physical, psychological, mental or psychosocial functioning:
   - Minimal score of 10 in the Health sub-scale of the OTI questionnaire; or HIV or HCV disease; or other chronic condition related to drug use by means of medical examination or blood test; OR
   - Minimal score of 41 and 54, men and women respectively, in the SCL-90 scale or psychological/psychiatric diagnosis of co-morbidity; OR
   - At least six separate episodes in the previous month of involvement in criminal activities (self-reported), and/or at least six days without personal contact (of at least half an hour duration a day) with a non-drug-using person, or unstable housing;

f. Injecting opioids in at least 8 months in the past 12 months;

g. Have been injecting opioids regularly in the last month (at least 4 days or more in a week);

h. At least two episodes of opioid addiction treatment (methadone maintenance, detoxification, residential care, etc), including one or more episodes of substitution treatment;

i. Willingness and ability to adhere to study protocol and follow-up schedule as determined through the pre-randomization period;

j. Documentation of fulfillment of the above study criteria (prison records, treatment records, cohort study enrolment, urine sampling); and

k. Provide written and informed consent.

9.2. Exclusion Criteria

Participants will be ineligible for Stage I if they do not meet the above criteria or if they meet any of the following exclusion criteria:

l. Diagnosis of severe medical or psychiatric conditions contra-indicated for diacetylmorphine or hydromorphone treatment.

m. Pregnancy upon study entry (Hydromorphone is a class C teratogen and should not be given to pregnant women. All female participants upon study entry will be urged to engage only in protected sexual intercourse and will provide consent to undergo monthly pregnancy tests during the course of the study);

n. Serum bilirubin >2.5 x normal;
Individuals will be eligible for Stage II provided they are still receiving Phase I injection medication at the treatment clinic. Participants will be excluded from Stage II if they meet any of the exclusion criteria above which may have changed since entry into Stage I. Participants who switch completely to other treatments or abstinence during Stage I will not be randomized to Stage II.

10.0 Removal of participants from therapy or assessment

Participants are free to withdraw from treatment and/or follow-up at any time and without giving any reason. If a participant decides to withdraw from treatment, the clinic staff and doctor will offer to make arrangements for accessing methadone maintenance therapy, detox, residential treatment or any standard drug treatment they wished to attend.

Violent behaviour in the treatment clinic or research centre and smuggling drugs out of the clinic can lead to treatment discontinuation. Staff members will be trained on non-violent crisis intervention in order to successfully handle any verbal or physical abusive behaviour toward staff members or participants on the clinic premises. Participants with serious adverse drug reactions might be also discontinued. Those who develop psychoses will be treated but will not be discontinued. Participant discontinuation from study treatment will be evaluated on an individual basis by the Clinical team.

Participants who are incarcerated or hospitalized during the treatment period generally received MMT from prison or hospital physicians. After the end of the incarceration or hospital stay, such participants are eligible to return to the clinic and re-enter their allocated treatment program.

No matter the disposition of the study participant with respect to treatment, the research team will make every effort to obtain follow-up assessments from all participants even when this requires interviews in jail or hospitals or if a participant had his/her treatment withdrawn.

11.0 Breaking the randomization code

SALOME is a double-blind trial, where neither participants, investigators (this includes anyone determining eligibility, evaluating endpoints, or assessing compliance with the protocol), or staff (who provide direct care to study participants), are aware of the treatment participants in SALOME were assigned at randomization and allocation. Only the site pharmacist will know which participants are receiving which drug. All prescriptions will be written up in mg DAM equivalence and the pharmacist is the one who will make the conversion, as required.
The reason to blind the study treatment allocation to the above mentioned parties is to limit the occurrence of bias in the conduct and interpretation of the trial arising from the influence which the knowledge of treatment may have on the recruitment and allocation of participants, their subsequent care, the attitudes of participants to the treatments, the assessment of endpoints, the handling of withdrawals, the exclusion of data from analysis, and so on. Maintaining the blind in the SALOME study is critical to prevent this bias. The essential aim of the blinding is to prevent identification of the treatments until all such opportunities for bias have passed. The blinding should be maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded.

Breaking the blind should be considered only in exceptional situations and only when the investigators and managers have deemed it absolutely necessary. In an emergency, and only in such cases, the Principal Investigators or his/her designate are authorized to contact the pharmacy to ask that the double-blind code be broken. In the NAOMI study, due to periodical pregnancy test, one participant was determined to be pregnant. The participant was switched to methadone and the code was broken for safety reasons given that hydromorphone is considered a teratogen (she was receiving DAM). There is the possibility that participants ‘guess’ their treatment allocation. Another unlikely possibility is that a participant performs a toxicological test to know the substance she/he is receiving. In any case, since the staff will not be aware of the assignment, nor ratification or denial will be possible.

Any intentional or unintentional breaking of the blind should be reported and explained at the end of the trial, irrespective of the reason for its occurrence. The procedure and timing for revealing the treatment assignments should be documented.

In general, deliberately breaking the blind may be reasonable in the following situations:

- Threats to participant safety: some severe adverse events may call for emergency treatment, which may require breaking of the blind. However, breaking the blind is not necessary for all emergent treatments.
- Threats to investigator safety: accidents that require knowledge of the participant's treatment (e.g., needle stick) to determine the risk and potential remedy.
- Regulatory reporting: SAE's in order to determine whether to report to the regulatory authorities
- Disclosing assignment to DSMB

12.0 Sample Size and Power Calculations

The intent of the study is to demonstrate non-inferiority in each stage. This approach requires setting out a priori a non-inferiority margin, denoted \( \Delta \), for the maximum difference allowed between the “new” treatment and the active comparator. One conventional method is to derive the margin as a proportion of the therapeutic effect of the active agent compared to placebo. However, recent European guidelines advise against this approach. It is recommended that the selection of the non-inferiority margin should include clinical judgement.

To derive \( \Delta \), we conducted a Delphi process in which we canvassed the leading investigators in the world with respect to heroin assisted therapy (van den Brink, Holland; Haasen, Germany; Haemmig, Switzerland; Uchtenhagen, Switzerland; Degkwitz, Germany). The decline in number of days of illicit...
heroin use has been remarkably consistent in HAT trials conducted to date: minus 20.1 days in Germany; minus 16.2 days in Spain; minus 20.6 days in NAOMI to date. The investigators were asked what margin they would tolerate in order to accept HDM or oral administration as non-inferior than HAT. Based on consensus from this international group, the inferiority margin has been set at 4 days.

For stage I, a non-inferiority trial with an expected decline of 20 days with a SD = 11.0 (data derived from the NAOMI results) from baseline, a margin of 4 days, a power of 0.90, an expected loss-to-follow-up rate of 0.05 and a one-sided alpha level of 0.05, requires 202 subjects (101 per group)\textsuperscript{75}. The confidence intervals were calculated based on normal approximation. Using the distribution of the decline in the number of days of illicit heroin in the prior 30 days from the NAOMI study and the sample size calculated for this proposed study, we conducted a simulation to assess the normality of the sample mean. Our simulation showed that normal based inference seemed to be reasonable and valid (Appendix II).

It is possible that the data for the primary outcome will not be normally distributed. If we use the binary outcome (decline to ≤ 3 days of illicit heroin use) defined as success, we can expect a success rate of 0.80 based on existing data. The margin of 4 days translates to a relative effect size of 0.80. For stage I, a non-inferiority trial with an expected success rate of 0.80, a lower margin set at 0.80 relative to expected, a power of 0.90, an expected loss-to-follow-up rate of 0.05 and a one-sided alpha level of 0.05, requires 194 subjects (97 per group). We can therefore safely utilize a sample size of 202.

With a sample size of N = 202, we can expect that approximately 172 participants will enter into phase II. Under the same assumptions as above, this will yield a non-inferiority trial with power = 0.86\textsuperscript{75}.

### 13.0 Drug Formulation and Storage

#### 13.1. Drug Formulation

Both study drugs, diacetylmorphine and hydromorphone will be procured from Almat and Galenova (distributors). Diacetylmorphine HCl (API) is manufactured by DiaMo, Switzerland. Hydromorphone is compounded at the study pharmacy from API produced by Macfarland Smith, UK. Hydromorphone could also being obtained from Sandoz Inc, Boucherville, Quebec.

All medications will be prepared by the onsite licensed pharmacy registered with the College of Pharmacists of British Columbia. This pharmacy will prepare powder ingredients in a particle containment hood and injectables will be prepared in a sterile laminar flow hood located within a Class 1000 clean room. The clean room, particle containment hood and laminar flow hood will be certified by 3rd party every 6 months. Canadian Society of Hospital Pharmacists standards will be used to prepare sterile injectables. GMP standards will be used to produce all study medications.

With regard to the oral preparations (not part of NAOMI), the pharmacies will follow the limited batch preparation of non-sterile products guidelines\textsuperscript{76-78}. Quality assurance guidelines state that the finished preparation should contain not less than 90% and not more than 110% of the theoretically calculated (intended dose) and labelled quantity of active ingredient per weight and not less than 90% and more than 110% of the theoretically calculated weight of the preparation. The preparation assay is done on site, the active assay is sent out for identification and potency testing. These oral medications are prepared according the mentioned best practice guidelines.
13.2. **Drug Transport and Storage**

Diacetylmorphine will be shipped by Almat to the on-site pharmacy where the medication will be stored in an appropriately secure area. Storage will be at room temperature in a TL-30 level safe until preparation. The injection solutions and oral liquid will be stored in a secure area at 2-8° C and protected from light. All study medications will be kept in a secure area in the clinic. Clinic is equipped with security monitoring and alarm systems.

Expiry dates will be monitored and counts will be strictly audited.

Outdated or unused medication will be destroyed by the pharmacist in accordance with Federal Regulations. Used needles and syringes will be disposed in accordance with WHMIS standards.

13.3. **Washout Period**

There is no washout period in this study.

14.0 **Diacetylmorphine, DAM**

14.1. **Pharmacology**

DAM is metabolized very rapidly after administration. When given by the enteral route, most of the diacetylmorphine may already have been metabolized to morphine by the time it reaches the opiate receptors. On the one hand, DAM is unstable and undergoes spontaneous hydrolysis; on the other hand, a certain amount of time passes before the drug is absorbed. Diacetylmorphine is considerably more lipophilic than monoacetylmorphine or morphine and is thus likely to cross the blood-brain barrier the fastest of the three.

DAM is deacetylated to 6-MAM (monoacetylmorphine) and morphine within a few minutes (2-30) by plasma cholesterolinases in the blood and liver cholesterolinases. After glucuronidation in the liver, the morphine is ultimately excreted in glucuronidated form primarily by the renal route (90%) but also by the hepatic route (10%). A small proportion of the fraction excreted hepatically can be hydrolysed in the gut and absorbed in the form of morphine via the enterohepatic circulation. Some of the substance is decomposed by demethylation to form traces of nomorphine. Morphine-6-0-glucuronide has been shown in animal studies to have twice the analgesic potency of morphine; when administered directly into the ventricles of the brain it is as much as one hundred times as potent.

The plasma binding of DAM is 40%, the volume of distribution 20-45 litres, the clearance from the blood 30.8±2.1 ml/kg BW/min.

DAM and its metabolites pass into breast milk and cross the placental barrier.

Between 42 and 70% of the substance is excreted renally. Most of the diacetylmorphine can be recovered from the urine in the form of glucuronidated morphine, primarily morphine-3-0-glucuronide. Morphine and nomorphine can also be detected, as can monoacetylmorphine, although only for a short time after intravenous administration. The decomposition products can be detected for between 2-4 days, although they have persisted for longer in some individuals. Caution must be paid, since active morphine glucuronides may accumulate in participants with impaired renal function.
14.2. **Known and Potential Risks**

*Effects and adverse effects of DAM*

The distinctions between the effect desired by the participant (the rush or flash), than sought by the therapist (to still the participant’s hunger for opiates) and the adverse effects (particularly intoxication) are blurred. DAM has no defined therapeutic range; it is used on an individual basis depending on the development of tolerance. The effects and adverse effects are dose-dependent and may change if tolerance develops.

The literature gives little information on the frequency of the adverse effects listed below. Most regularly occurring adverse effects tend to be harmless (e.g. constipation, dry mouth). Some adverse effects occur exceptionally rarely, and many have been described only in connection with the illegal consumption of heroin. Most of the adverse effects listed below were not seen during a six-year observation period covering more than 1,700 participants to date. They have nonetheless been included for the sake of completeness and to draw the attention of prescribing physicians and other medical personnel to this aspect.

To some extent the number and nature of effects and adverse effects correlate with the degree of heroin habituation, i.e. they tend to become less frequent and less intense. This effect is anticipated particularly with regular administration and constant dosing, as is the case in therapy centres. Illegal heroin consumption, in contrast, is characterized by the constant alternation of withdrawal and intoxication phases, and the presence of acetylcodeine, a variety of adulterants and the addition of other psychotropic substances – which of course make the development of serious side effects more likely.

*Effects*

Euphoria, analgesia, tranquillizing effect, unspecific antipsychotic effect, anxiolysis, antitussive action, prevention of withdrawal symptoms in participants habituated to opiates.

*Adverse effects*

The most frequently observed adverse effects are the classic side effects of opiates, i.e. constipation, nausea and histamine-mediated side effects, plus sedation, particularly if sedating substances are also consumed. More serious adverse effects have been reported in the form of epileptic seizures, thrombocytopenia, loss of consciousness, arrhythmias and orthostatic collapse. A systematic listing, irrespective of frequency, includes the following:

a) Central nervous system: sedation, nausea, vomiting, headache, dizziness, miosis (which can lead to impaired vision in conjunction with far-sightedness), reduced libido, impaired concentration, impaired cognitive function and reaction speed, EEG changes, respiratory depression (with reduction of respiratory frequency and volume, leading to hypoxaemia), disturbed appetite regulation.

b) Autonomic nervous system, gastrointestinal and urogenital systems: sweating, constipation, raised pressure in the common bile duct and gallbladder, dry mouth, urinary retention, effects on liver and kidney function, sexual dysfunction.
c) Histamine-mediated adverse effects: pruritus, urticaria, facial reddening, localized or generalized reddening, swelling of the extremities, facial swelling (angioneurotic oedema).

d) Cardiovascular system and respiratory tract: bradycardia, extrasystoles, hypotension, fainting, peripheral vasoconstriction, pulmonary oedema, bronchial constriction, status asthmaticus.

e) Other adverse effects: changes in the immune system, loss of muscle tension, altered core temperature (hypothermia or hyperthermia), tongue discoloration, various endocrinological changes (hypothalamic-pituitary-gonadal axis and stress axis, ADH), tolerance development, mental and physical dependence.

f) The following disturbances have also been described in the literature in connection with heroin use: leukoencephalopathy, epileptic seizures, cerebral ischaemia, spinal myelopathy, myoclonia, peripheral plexopathy and neuropathy, non-traumatic rhabdomyolysis, cardiomyopathy, myocardial infarction, thrombocytopenia.

Intoxication

Clouded consciousness, coma, apnoea, severe hypoxaemia (these adverse effects may lead secondarily to traumatic rhabdomyolysis, pressure neuropathy with muscular paresis, hypoxaemic organ damage), pulmonary oedema, cardiovascular arrest, death. Marked miosis and an overfilled bladder are diagnostic. In individuals not habituated to opiates the potential lethal dose of diacetylmorphine is 30 mg when given intravenously and 100 mg when given orally.

Withdrawal symptoms

Yawning, restlessness, craving, tremor, shivering, sweating, running nose, muscle cramps, pain, nausea, vomiting, diarrhoea, anxiety, raised temperature, loss of appetite, impaired sleep, tachycardia, arterial hypertension. Withdrawal symptoms start around 6 hours after the last dose and last up to a week.

Interactions

Potentiating effect on the sedating and muscle-relaxing action of muscle relaxants. Concomitant use of hypnotics and some neuroleptic agents can lead to a major increase in sedation and respiratory depression. Interactions have also been reported with some drugs used in antiretroviral therapy (see below).

Restrictions on use and precautions

a) Prescription of DAM to individuals hypersensitive to DAM is contraindicated.

b) Caution is recommended in participants with: renal failure, hepatic failure, respiratory diseases, organic brain disorders or cerebral trauma. Little information is available on use in pregnant women or nursing mothers and on possible teratogenic effects or possible late complications in affected children.

c) Under no circumstances should substitution therapy be combined with antidepressant therapy involving MAO inhibitors, e.g. moclobemide.
d) Individuals receiving therapy with diacetylmorphine should be advised against driving and working off the ground or on dangerous machinery.

e) For participants with certain underlying diseases, such as cardiac conduction disorders, genuine or post-traumatic epilepsy, hypothyroidism, adrenal failure and others, careful consideration should be given to whether the benefits of therapy outweigh the possible risks.

f) Appropriate precautions should be taken for individuals who additionally consume alcohol, benzodiazepines, methaqualone, barbiturates, GHB and other centrally acting sedatives.

**Points to consider with additionally prescribed medication**

a) Various drugs interact with DAM or cause an increase in the adverse effects. Additionally prescribed drugs should therefore be selected carefully from each therapeutic group with special consideration of their side effects. The following list covers the most important categories:

b) Antidepressants: Tricyclic antidepressants, in particular, can trigger cardiac conduction disorders, reduce the seizure threshold or cause changes in the thyroid hormones. In case of doubt, ECG/EEG examination and monitoring of thyroid parameters are advised. Some SSRIs, such as fluoxetine (Fluctine®) and fluvoxamine (Floxyfral®) may affect the breakdown of methadone, and this should be borne in mind when switching participants to methadone or co-medicating with methadone.

c) Neuroleptics: Here, too, the possibility of EEC changes and a reduction in the seizure threshold must be borne in mind, for example with clozapine (Leponex®). Neuroleptics may also have a powerful sedating action. In case of doubt, EEG examination is advised.

d) HAART (highly active antiretroviral therapy): Ritonavir (Norvir®) is thought to have a marked effect on the serum concentration of DAM, reducing it by 50%. On the other hand, increased permeability of the blood-brain barrier has also been reported. Interactions with other antiretroviral substances all have a question mark beside them. Nevirapin (Viramune®) and ritonavir (Norvir®) can cause a marked reduction in serum levels of methadone, and in both cases a dose adjustment of up to 45% may be necessary (information from HIV Clinic, Zurich University Hospital).

e) Benzodiazepines: Benzodiazepines which are unknown or not very common in the drug scene are generally the better choice. Preference should also be given to benzodiazepines which are absorbed more slowly and have longer half-lives, such as diazepam (Valium®), clonazepam (Rivotril®), prazepam (Demetrin®), clobazamun (Urbanyl®). Cumulative sedation can be avoided by administering prescribed benzodiazepines at the same time as or immediately after DAM.

f) Antiepileptics: Barbiturates often prove problematic because of their sedative effect. If long-term therapy with barbiturates or benzodiazepines is medically unavoidable to treat epilepsy, the participant must be observed and the dose of DAM must be adjusted as necessary.

14.3. **Compliance Monitoring and Safety Strategies**

Every effort will be made to ensure the safety of participants in the study. The NAOMI trial has provided excellent experience regarding safety issues. In SALOME, participants will have an assessment period of 20 minutes before (5 min) and after (15 min) the intake of the medications.
period allows monitoring and treatment of possible adverse reactions. After 110,000 injection episodes at NAOMI, most of the adverse events (AEs) registered were expected as part of known opioid side effects and reactions due to the route of administration. More than half of the AEs were skin and soft tissue infections, mainly moderate and mild allergic reaction (facial flushing, pins and needles, and generalized urticaria; localized itchiness, raised blotchiness at injection site). The two most frequent severe AEs at least possibly related with the injection medication were overdoses (11) and seizures (7). When injected opioids are taken under the supervision of health care staff, overdoses and seizures have been shown to be effectively controlled and restored. This has been also the case in the NAOMI study in which all episodes of oversedation responded immediately to oxygen and naltrexone. In no case was the participant admitted to hospital and none of the AEs required the discontinuation of the treatment.

Methadone can also be prescribed by the addiction physicians at the Clinic where the study is going to be conducted. All the physicians at the clinic are licensed to prescribe methadone. Also, the on-site pharmacy is licensed to deliver methadone by the British Columbia College of Pharmacist.

Compliance monitoring will be undertaken with this goal in mind. Safety measures in the study clinic will include:

All oral doses will be prepared in liquid form, diluted with a sweetened solution with the goals of masking the bitter taste, making injection less likely and discouraging diversion.

All doses of study medications will be administered under direct observation.

As described above, steps will be taken to assist participants in finding injection sites on the upper extremities, thighs and gluteals and to educate participants about safe injection sites and practices. Participants will also receive printed material on safe injection procedures.

At the study clinic, safe injection facilities will be established for participants receiving injectable medications that will be staffed by health care professionals and equipped with adequate equipment to handle any overdoses that may occur. The staffing, equipment and procedures for these facilities will be built over the experience during the NAOMI study. All staff will receive comprehensive training on appropriate participant monitoring and handling in order to prevent overdose (e.g., monitor the participant for continual, regular breathing, keep participant awake). In addition, oxygen will be available at all sites.

All participants will receive medical evaluation of their health status and a rigorous protocol for incremental alteration in the dosing of the medication to minimize the potential for overdose.

All participants will be required to pass a pre- and post-injection assessment before receiving their medication and before leaving the clinic. After participants take medication, they remain at the clinic for at least fifteen minutes and receive post-injection assessments to assure that they are not released with impaired motor functioning. This waiting period will also help to prevent overdoses as the participants will be carefully monitored during this waiting period.

Staff dispensing medication will be trained and equipped to perform breathalyzer testing on any participant who appears impaired or intoxicated and to not medicate those whose blood alcohol level is equal to or greater than 0.05. Methadone dose will be reassessed based on the degree and cause of the impairment.

Unused needles and syringes will be maintained in a locked storage cabinet and clinic staff will keep an inventory of their use. In addition, needle safety handling procedures for work related
to infectious agents and individuals in these high-risk populations will be developed and distributed to all clinic staff.

Should the research staff at any time become aware of behaviour or other circumstances which indicate a risk of harm to the study participant or to others, this information will be communicated to the Principal Investigators. They will determine whether further action, including communication of the information to the clinical staff responsible for the care of the subject, is required. Such events will be fully documented by the Principal Investigators.

The clinic will have an alcohol breath analyzer available to monitor blood alcohol levels, before medication is dispensed as needed.

15.0 Treatments to be administered

Treatments include diacetylmorphine and hydromorphone, injected or oral. Diacetylmorphine and hydromorphone will be administered on a double-blind basis.

The pharmacological profile of hydromorphone is similar to that of DAM. A study carried out on cancer patients in the post-operative phase showed that the analgesic effect and elimination curve are similar. The side effect profile is also similar with the exception of rash, which was more common with DAM, and headaches, which were more common with hydromorphone. Hydromorphone was shown to be 3.3 times more potent for analgesia than DAM 54. However, in the NAOMI study (the only one testing HDM for substitution treatment) a ratio of 2:1 for agonist maintenance treatment was observed for DAM to HDM 69.

Diacetylmorphine and hydromorphone, either orally or injected, can only be prescribed and self-administered in the study clinic under supervision. DAM and HDM can be self-administered by injection or orally up to three times daily. Medication dosage will be prescribed in DAM-equivalent mg, based on the Swiss clinical practices47 and the experiences during the NAOMI trial.

Participants can at any time switch partially or totally to oral methadone if deemed appropriate. Oral methadone can be prescribed by study doctors or by other physicians (if the participant is not receiving the study drugs). Oral methadone will be prescribed in accordance with the College of Physicians and Surgeons of British Columbia' guidelines. Methadone prescription would be transferred to another doctor when the participant has stopped receiving DAM or HDM. This would avoid two unrelated doctors simultaneously prescribing opioids for maintenance. Dispensing of oral methadone can be at the study site (at the on-site pharmacy), community pharmacies, or other settings (e.g., other community clinics). Methadone will be ingested either once or twice daily. Methadone dosages will be based on best practices and current clinical practice guidelines 9.

Study treatments will be provided for 12 months followed by a 1-month period during which participants still being treated with DAM or HDM will be tapered and transitioned to conventional therapies such as methadone. The 6 and 12-month study visit at which the primary outcome measures will be assessed will be conducted before any tapering or transition began.

Upon entry into the program, each client will be assigned a psychosocial support worker whose duties will be to establish a relationship with the participant, perform an overall assessment of the individual’s situation and psychological and social needs, and suggest appropriate services. Throughout treatment,
support workers will meet intermittently with participants to provide lifestyle counselling or
counselling about risk behaviour, intervene in emergency or crisis situations and, when necessary, help
to provide access to housing, social programs, childcare or parenting skills development, education or
professional training programs or legal services. Counselling staff will also provide cognitive-
behavioural therapy-based interventions for mental health problems including structured relapse
prevention for drug use as clinically appropriate.

In addition to the case management functions provided by the psychosocial support worker, all clients
will have access to a defined range of primary care services matched to the prevalent conditions seen in
injection drug users. These included nursing supports such as wound care and immunizations,
identification and treatment of acute infections and acute psychiatric symptoms, screening for blood-
borne pathogen infections (and where required support to initiate or adhere to antiretroviral
medications) and medication management for psychiatric or other required medications. In keeping
with the Health Canada Best Practices documents for methadone maintenance, all services will be
delivered in a patient-centred fashion ⁹. The multidisciplinary clinical team will meet weekly to review
and revise individualized care plans.

The study site has an on-site pharmacy that only serves the clinic clients. This pharmacy is fully
licensed by the College of Pharmacist of British Columbia. The pharmacy carries several medications,
including benzodiazepines. Medications can be stored in a locked cabinet in the dispensary (for daily
operation), in a fridge or in a safe in the vault. The pharmacy operates under the BC College of
Pharmacist guidelines.

15.1. Selection of dosages in the study

Due to high inter-individual variability, there are no fixed rules for the dosage of DAM in maintenance
therapy for opioid-dependent individuals. Over the years, the various therapy centres offering heroin-
assisted treatment have developed a regimen for initial titration, maintenance and conversion of DAM
into methadone. The upward titration at the start of therapy in the trial always begins with a safe dose
and will follow the protocol developed for the NAOMI trial. Maximum DAM dosages are based on the
Swiss clinical studies ⁴⁷.

Dosages of oral DAM and injectable and oral HDM will be calculated using the proportions based on
experimental and experiential evidence from the Swiss heroin-assisted treatment studies as well as
NAOMI. On these Swiss studies, 1 mg of injected DAM are equivalent to 3.3 mg. of oral DAM ⁶¹. In
the NAOMI study, the ratio between injected DAM and HDM was of 2:1 ⁶⁹.

The initial adjustment of the medication dose will be done over a three-day period as described below.
In describing NAOMI drug dosage, we refer to injectable DAM equivalents in order to maintain the
double-blind.

100 mg DAM = 100 mg DAM injection = 50 mg HDM injection = 330 mg DAM oral = 165 mg HDM oral

Diacetylmorphine and Hydromorphone
Titration process:
For participants not receiving substitution treatment, the titration protocol for injectable and oral formulations will be the same.

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

The following titration protocol is based on doses expressed as DAM-Equivalents.

Day 1
Dose 1: Give 15 mg, wait 15 minutes. If no intoxication, add 30 mg more. Observe for 30 minutes after second dose then have participant leave and return at next dosing window period.
Dose 2: If earlier doses were well tolerated, give 45 mg. Wait 30 minutes. If no intoxication and subject so wishes, give 30 mg more. Observe for 30 minutes after second dose then have participant leave and return at next dosing window period.
Dose 3: If earlier doses were well tolerated, give 75 mg. Wait 30 minutes. If no intoxication and subject so wishes, give 30 mg more. Observe for 30 minutes after second dose then have participant leave and return next day.

Day 2
Dose 1: Administer 40% of the total daily dose at Day 1 (up to a total of 90 mgs if tolerated all possible doses on first day) Wait 30 minutes. If no intoxication and subject so wishes, give 30 mg more. Observe for 30 minutes after second dose then have participant leave and return at next dosing window period.
Dose 2: Administer the maximum tolerated amount of Dose 1 (i.e. up to 120 mg). Wait 30 minutes. If no intoxication and participant so wishes, give 30 mg more.
Dose 3: Administer the maximum tolerated amount of Dose 2 (i.e. up to 150 mg). Wait 30 minutes. If no intoxication and participant so wishes, give 30 mg more.

Day 3
Administer the maximum tolerated amount at Day 2 for the 3 doses on Day 3. After consulting with the physician, adjust the dosage once a week until the subject feels comfortable and does not show any excessive intoxication or respiratory depression or until the maximum dose is reached (400 mg/dose or 1000 mg/day). Doses cannot be increased on weekends.

Pre and post intake assessment
The pre-intake assessment will occur 5 minutes after arrival of each participant and can only be done by one of the nursing staff. The purpose of this assessment is to ensure that the participant is not intoxicated (including centrally acting sedatives and cocaine) or in any other acute clinical condition that would contraindicate use of the study medications (for example, intoxication due to the abuse of...
cocaine resulting in the participant being actively psychotic or agitated in a way that would be an immediate safety risk). Participants can choose intravenous, intramuscular or subcutaneous injection; injections are only allowed in the upper extremities, thighs, and gluteals. In thighs and gluteals, participants can only inject intramuscular or subcutaneously.

The post-intake assessment could be done by any health care provider who has completed the assessment training by the study Clinic Lead Physician, with the understanding if there were any doubts or uncertainty about a participant’s assessment, they must be referred to a nurse to do the post-assessment. After 15 minutes, participants can leave the clinic if they are deemed fit.

Combining diacetylmorphine and methadone

As noted above, participants are eligible to receive methadone if clinically indicated (for example, to avoid withdrawal symptoms between opioid injections). Methadone doses will be individually adjusted by physicians based on participants' requests and responses. The participants will obtain the methadone from the nurses or pharmacists in the treatment clinic or in community pharmacies who have been trained to supervise participants taking methadone.

Diacetylmorphine and methadone dosage equivalence

It is critical to establish a conversion factor for switching from methadone to DAM and vice versa. The objective is to maintain the average degree of saturation of the opiate receptors by opiates in order to prevent withdrawal symptoms and thus supplementary consumption of illegal drugs on the one hand and to avoid overdosage due to accumulation on the other.

When converting dosages, the opiate bioavailability of the individual pharmaceutical agents must also be borne in mind. A 100% bioavailability of DAM injectable solution is assumed, irrespective of whether it is administered intravenously, subcutaneously or intramuscularly. The calculation is always based on the intended effective opiate dose.

Based on these assumptions and years of experience, the Lifeline and Crossline treatment centres in Zurich have developed a conversion table, which has been refined continually and used with success 47, including during the NAOMI trial (Table 1). The conversion should be based on doses received, not prescribed.

Table 1: Conversion table for injected diacetylmorphine to oral methadone, daily dose in milligrams.

<table>
<thead>
<tr>
<th>DAM</th>
<th>Methadone</th>
<th>DAM</th>
<th>Methadone</th>
<th>DAM</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>20</td>
<td>341-360</td>
<td>100</td>
<td>681-700</td>
<td>135</td>
</tr>
<tr>
<td>21–40</td>
<td>20</td>
<td>361-380</td>
<td>105</td>
<td>701-720</td>
<td>140</td>
</tr>
<tr>
<td>41–60</td>
<td>20</td>
<td>381-400</td>
<td>105</td>
<td>721-740</td>
<td>140</td>
</tr>
<tr>
<td>61–80</td>
<td>25</td>
<td>401-420</td>
<td>110</td>
<td>741-760</td>
<td>140</td>
</tr>
<tr>
<td>81–100</td>
<td>30</td>
<td>421-440</td>
<td>110</td>
<td>761-780</td>
<td>145</td>
</tr>
<tr>
<td>101–120</td>
<td>35</td>
<td>441-460</td>
<td>110</td>
<td>781-800</td>
<td>145</td>
</tr>
<tr>
<td>121–140</td>
<td>40</td>
<td>461-480</td>
<td>115</td>
<td>801-820</td>
<td>150</td>
</tr>
<tr>
<td>141–160</td>
<td>50</td>
<td>481-500</td>
<td>115</td>
<td>821-840</td>
<td>150</td>
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<tr>
<td>161–180</td>
<td>60</td>
<td>501-520</td>
<td>120</td>
<td>841-860</td>
<td>150</td>
</tr>
<tr>
<td>181–200</td>
<td>65</td>
<td>521-540</td>
<td>120</td>
<td>861-880</td>
<td>150 (160)</td>
</tr>
</tbody>
</table>

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The figures in the high-dose range are the target dose and the dose (in brackets) which can be reduced to 150 mg during the 1-3 days before departure.

Switching from injectable to oral diacetylmorphine/hydromorphone

After six months of treatment, participants still receiving injectable medications will be randomized to either continue receiving injectable medication or to switch to an oral formulation. The conversions from injectable to oral medication are calculated assuming a ratio of 1:3.361 however the titration process ensures participant safety and individualized dose adjustment. All doses are expressed in mg injectable DAM-equivalent.

The transition from injectable to oral formulations will take place over a 7 day period. This is intended to help participants to gradually leave the injectable route of administration, allowing a more smooth transition. However, under consultation with the physician, participants can choose the make this transition quicker (especially those with difficulties injecting the medications). Also, at any time a physician, nurse or the participant itself may order a lower dose or more gradual titration.

Day 1:

Participants will continue injecting the medication in the first and last dosage of the day. The second dosage will be oral. Participants will receive half of their injection dosage or 60mg1 whatever is less. Wait 30 minutes. If no intoxication and subject so wishes, give 30 mg more. Observe for 30 minutes after second dose then have participant leave and return at next dosing window period.

Day 2:

Participants will continue injecting the medication in the first and last dosage of the day. The second dosage will be oral. Participants will receive the total oral dosage of the prior day (i.e. up to 90 mg). Wait 30 minutes. If no intoxication and participant so wishes, give 30 mg more. Observe for 30 minutes after second dose then have participant leave and return at next dosing window period.

Day 3:

Participants will continue injecting the medication in the first and last dosage of the day. The second dosage will be oral. Participants will receive the total oral dosage of the prior day (i.e. up to 120 mg). Wait 30 minutes. If no intoxication and participant so wishes, give 30 mg more. Observe for 30 minutes after second dose then have participant leave and return at next dosing window period.

Days 4:

1 Half injection dose or 60mg is the DAM equivalent dose and will be converted to oral
Participants will continue injecting the medication in the first and last dosage of the day.

The second dosage will be oral. Participants will receive the total oral dosage of the prior day (i.e. up to 150 mg). Wait 30 minutes. If no intoxication and participant so wishes, give 30 mg more. Observe for 30 minutes after second dose then have participant leave and return at next dosing window period.

Days 5 and 6:

Participants will continue injecting the medication in the first dosage of the day.

The remaining doses will be taken orally, in the dosage established on Day 4 (i.e. up to 180 mg).

Day 7:

Participants will receive all doses of their medication orally. Administer the maximum tolerated amount at Day 4 for the 3 doses on Day 3 (i.e. up to 180 mg). After consulting with the physician, adjust the dosage once a week until the participant feels comfortable and does not show any excessive intoxication or respiratory depression or until the maximum dose is reached (400 mg/dose or 1000 mg/day). Doses cannot be increased on weekends.

Oral titration process for participants not transitioning from injectables:

For participants being titrated to oral study medications but not transitioning from injectable treatment (e.g., being hospitalized and coming back to the oral arm from the street or methadone), the titration protocol will be in three days (instead of seven, when they transition directly from injectables). Although the conversion ratio for oral to injectable is 3.3:1, preliminary data has shown that after titration to best clinical dose, is more likely to be 2/2.5:1. This oral titration protocol is based on the 3 days titration for injectables. Given the different pharmacokinetics of the oral (slower than injectable), the doses in this titration protocol are based on a more conservative 2:1 ratio (versus 3.3 to 1) oral to injectable. After titration, doses will be adjusted in the following weeks, according to dose prior the participant's absence, if necessary.

This oral titration 3 days procedure is for participants that have already been titrated to oral under the 7 days procedure and have had a regular oral dose but have left treatment and are returning to oral after a more than 7 days absence. Is also to be used for cases where a participant is transitioning directly to oral after an absence from study medication. This would be the case when a participant is in jail or hospital at the time of randomization, or when a participant decides not to start oral at the time of randomization but changes his/her decision after being off study treatment more than 7 days.

At any time during the titration period, a physician or nurse may order a lower dose or more gradual titration based on participant response and safety concerns. In order to allow flexibility, the participant itself can also request a lower dose or a more gradual titration process, such as only upping by 10 mg, not taking a second dose, etc. For safety reasons, the last dose of the day will not be increased.

The following titration protocol is based on doses expressed as injectable DAM-Equivalents (the participant receives 3.3 times more mgs).

Day 1
Dose 1: Give 10 mg, wait 30 minutes. If no intoxication, add 20 mg more. Observe for 30 minutes after second dose then have participant leave and return at next dosing window period.

Dose 2: If earlier doses were well tolerated, give 30 mg. Wait 30 minutes. If no intoxication and subject so wishes, give 20 mg more. Observe for 30 minutes after second dose then have participant leave and return at next dosing window period.

Dose 3: If earlier doses were well tolerated, give 50 mg. Observe for 30 minutes, then have participant leave and return next day.

**Day 2**

Dose 1: Administer 40% of the total daily dose at **Day 1** (up to a total of 50 mg if tolerated all possible doses on first day) Wait 30 minutes. If no intoxication and participant so wishes, give 20 mg more. Observe for 30 minutes after second dose then have participant leave and return at next dosing window period.

Dose 2: Administer the maximum tolerated amount of **Dose 1 of Day 2** (i.e. up to 70 mg). Wait 30 minutes. If no intoxication and participant so wishes, give 20 mg more.

Dose 3: Administer the maximum tolerated amount of **Dose 2 of Day 2** (i.e. up to 90 mg). Observe for 30 minutes, then have participant leave and return next day.

**Day 3**

Dose 1: Administer the maximum tolerated amount at Day 2. Wait 30 minutes. If no intoxication and subject so wishes, give 20 mg more. Observe for 30 minutes after second dose then have participant leave and return at next dosing window period.

Dose 2 and 3: Administer the maximum tolerated amount of **Dose 1 of Day 3**. Observe for 30 minutes, then have participant leave and return at next dosing window period.

After consulting with the physician, adjust the dosage once a week until the participant feels comfortable and does not show any excessive intoxication or respiratory depression or until the maximum dose is reached (400 mg/dose or 1,000 mg/day). Doses cannot be increased on weekends or at the third dose of the day.

*Switching from oral to injected diacetylmorphine/hydromorphone*

Participants randomized to receive oral formulations in Stage II cannot switch back to injectable medications during the study protocol.

*Switching from diacetylmorphine/hydromorphone to methadone*
Switching to methadone and stopping DAM/HDM can be done under the following circumstances: incarceration, hospitalization, travel, or at the request of the subject. In such instances, it is preferable to spread out the procedure over several days. During this process, no benzodiazepines should be prescribed. In cases where a benzodiazepine is essential (e.g. alcohol withdrawal, long-term use of benzodiazepines), the minimum dose to prevent withdrawal symptoms should be used, additional care should be taken when increasing doses and the subject should be closely watched.

**Switching from methadone to diacetylmorphine/hydromorphone**

In specific situations, participants that switch to oral methadone can switch back to DAM (or HDM). These special cases primarily involve absences during which the participant cannot receive the study medications such as incarceration, prison, trips away, working away from home, etc. In such instances, the titration procedure is basically the same as the initial titration procedure described above. The target dosage after the switch will be generally the same as that prescribed before the participant’s absence. As mentioned above, the main risk in switching is an accidental overdose. Before the switch is initiated, the available information and the participant’s condition will also be considered (state of health, intoxication).

**Methadone**

For MMT treatment, we will follow the recommendations issued by the College of Physicians and Surgeons of each of the provinces concerned as to proper dosage, recommended urine testing and participant drug management (take home doses). In British Columbia, the methadone can be dispensed during the week from the treatment clinic and on the weekends by a community pharmacy. The methadone will be diluted in a solution to mask the drug’s bitter taste, to discourage the practice of injecting the drug and to prevent the risk of diversion.

Participants enrolled in the study are eligible to receive methadone concurrently with DAM or HDM if clinically indicated and also to switch completely to methadone treatment. Individuals who chose to switch to oral methadone alone and stop the study medications can receive take home doses if they meet the requirements according to the provincial standards.

Doses after periods not receiving the study medication

Participants, after not receiving the study drugs for a certain period of time, are allowed in some cases, to re-start treatment. They can do so if they are still in their six month participation window for each phase and if deemed appropriate by the physician (see Research and Clinical Operating manuals for details). If the participant did not receive the study drugs for more than 3 days (9 sessions) and less than or equal to 7 days (21 sessions and under) will receive 1/3 prescribed dose + 25 mgs each following dose until tolerated dose is achieved. If the participant did not receive the study drugs for more than 7 days (22 sessions) he will be re-titrated.

**15.2. Rescue Medication and Risk Management**
Although the study medications will be self-administered by the study participants, a registered nurse will be on duty at all times in the injection room. Furthermore a crash cart containing naloxone and oxygen will be available.

15.3. **Concomitant Medication**

There will be no restrictions placed on the administration of other concomitant medications (as clinically necessary) during the duration of the study except for medications with opioid antagonist or partial agonist properties. These will be contraindicated during the period of agonist maintenance.

15.4. **Psychosocial Components**

a) The medical and psychosocial services offered to participants in both arms of the trial will be identical and will be evidence-based, where possible

b) Every participant will have a complete psychosocial assessment at treatment entry which will identify active problems in the areas of mental health, drug use, housing, legal involvement and social functioning

c) A treatment plan will be developed in conjunction with the participant to address the identified problem areas

d) Each contact with a study physician (1-4 week intervals depending on the functional stability of the participant as described in the Ontario MMT Guidelines) may include a motivational enhancement intervention. The goal of these motivational enhancement interventions will be to increase the participant’s engagement with their assigned therapist

e) The physician and assigned therapist will review the treatment plan of each participant at least every three months and revise treatment goals in conjunction with the participant to reflect changing needs

f) Additional contact with the therapist will be elective and will address active issues for the participant, including case management, assistance with addressing housing issues, assistance accessing social benefits, brief cognitive behavioral counseling for relapse prevention

g) Referral to community agencies or other treatment resources available at the institutions participating in the studies will be offered for additional medical, psychiatric and drug treatment services as needed (for example, hepatology for chronic viral hepatitis, HIV primary care, psychiatric care for depression, residential addiction treatment for cocaine dependence, etc.) Continued participation in the study treatments will not be dependent on acceptance and attendance at these referrals.
16.0 Study Procedures

16.1 Recruitment

Our method of recruitment will include displaying and distributing program materials, for example brochures, flyers, and cards, and will be distributed and displayed in health and social service organizations (which serve our target population), such as at the needle and syringe exchange sites, public health departments, drug user associations, the Vancouver supervised injection site, community pharmacies, soup kitchens, etc. Recruitment will also rely on friends and associates of the target population via word of mouth (snowballing) contact. Finally, informal and formal contacts with individual professionals and those representing key institutions will be considered for referrals. These methods have been developed and refined over the course of the NAOMI trial. Specific barriers to both recruitment rates and methods have been identified and addressed in the protocol development. The majority of the HAT trials to date have reported slower-than-expected recruitment rates\cite{50,79-81}. This was also the case for NAOMI in which the recruitment period had to be extended significantly\cite{65}. However, there is a critically important difference in the inclusion/exclusion criteria between NAOMI and the proposed SALOME. In NAOMI, individuals who were currently in an MMT program or who had recently been in MMT in the prior 6-months were excluded. In SALOME, such individuals are eligible if they are currently using injecting illicit opioids. We expect this change to have a significant effect on recruitment. Over the course of NAOMI, a total of 1588 individuals initially volunteered to participate but 1337 were screened out, leaving 251 randomized. NAOMI recruitment data suggest that approximately 325 individuals of those screened out, would have met the SALOME criteria. For this reason, we are confident that the pace of recruitment into SALOME will be about double that observed in NAOMI, or 20 participants per month. It is noteworthy that at such a pace, it is not recruitment per se but clinic capacity that acts as the rate-limiting factor.

16.2 Pre-study Screening

All participants will provide informed consent prior to any study procedures being performed. Participants will then enter a screening period during which all necessary eligibility criteria will be determined and confirmed.

During screening, duration of drug history will be corroborated through reports from at least one of the following: criminal justice records, hospital and treatment records, and family members. Methadone maintenance and detoxification facilities will be contacted to confirm treatment history.

All enrolment procedures will be conducted according to a protocol and documented to provide consistent and accurate entry and to allow comparison of those who are and are not eligible for the study. Those who do not meet eligibility criteria for the study will receive a referral to a standard treatment program.

Once eligibility is confirmed and baseline evaluations performed, eligible participants will then be randomized into one of the treatment arms. The consent will include permission to track participants who drop out of the treatment component.
16.3. Outcome Assessment Research Visits

Participants will have research assessments performed during the pre-randomization period, at baseline, and at 3, 6, 9, 12, 18 and 24 months following initial randomization (see table 2). Research evaluations will be performed at a separate site from the treatment clinic. The baseline research interview will be performed by the research team prior to treatment assignment to reduce bias in self-reporting.

Apart from the daily or weekly visits to the treatment clinic for medication, study participants will return to the research centre and be requested to participate in subsequent follow-up outcome interviews/assessment every three months during the first year and at 18 months.

All self-reported outcomes data collection with the study participants will occur in a face-to-face, fully confidential interview setting at the research centre. The interviews will be conducted by trained field research interviewers, who are not part of the clinical treatment team, using standardized instruments. These include: Baseline and follow-up European version of the Addiction Severity Index (EuropASI)\(^46\); EQ-5D (EuroQoL)\(^82,83\); Opioid Treatment Index (OTI)\(^84\); SCL-90-R \(^85\); Maudsley Addiction Profile (MAP) \(^86\); and Health Utilities Index (HUI)\(^87\). To maximize the completion of the research evaluations study participants, whether or not retained in the treatment, will be compensated with a stipend of $25 for participating in the research component. Urine and blood samples for research purposes will be obtained at the clinic but the clinical staff will not have access to these results. It is important to note that the financial compensation is in place for research follow-up and not for treatment compliance. It will be made clear that a participants’ treatment status will not impact their participation in the research portion of the study.

The medical examinations will include the basic health indicators, the physical complications of substance use, urine screens and infectious diseases and STDs counseling. Female participants in the injectable opioid segment will receive monthly pregnancy tests, as heroin and hydromorphone are FDA-classified teratogens.

The success of the blinding will also be evaluated in agreement with the CONSORT\(^88\) recommendation to report “how the success of blinding was evaluated” for RCTs. The method to assess the success of blinding for participants, care providers, data collectors, and outcome assessors will follow the recommendations of Boutron et al.\(^89\): a) assessment of blinding early in the first days of the study and before the evidence of efficacy; b) participants will be allowed to express uncertainty; c) reporting results for both groups and d) include the guessing of the treatment assignment in the data analysis.

<table>
<thead>
<tr>
<th>Assessments</th>
<th>S(^{(a)})</th>
<th>T0</th>
<th>W1</th>
<th>T3</th>
<th>T6</th>
<th>W2(^{(b)})</th>
<th>T9</th>
<th>T12</th>
<th>T18</th>
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Table 2: Research Time Points and Planned Data Collection
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EuropASI = European Addiction Severity Index; FTND = Fagerstrom Test for Nicotine Dependence; OTI = Opiate Treatment Index; MAP= Maudsley Addiction Profile; SCL-90-R = Symptom Checklist-90-Revised; EQ-5D = EuroQol; CSQ = Client Satisfaction Questionnaire; HUI = Health Utilities Index; ARS = Adjective Rating Scale; VAS = Visual Analog Scale.

(a) Screening for eligibility will be carried out over three phases: signing consent forms and self-reported inclusion criteria, baseline evaluations and physical examination for final verification of medical exclusion criteria. Some criterion requires verification that will be done between screening phases. Therefore, screening times may vary.

(b) Only for those allocated to the oral arm

(c) Scores for MAP Physical and Psychological symptoms will be collected from the OTI and SCL-90-R.

(d) Hep A/B test at baseline only. HIV & HCV testing on follow up only for those who have tested negative at baseline. Baseline and 6 months test are part of inclusion and exclusion criteria confirmation. Following tests are standard of care and not collected in the research database.

**16.4. Medical Examination**

Eligible and consenting study participants will undergo a medical examination, which will include the following items:

a) Complete medical history
b) Family history of substance use disorders and significant medical conditions
c) Basic health indicators/vital signs (e.g., temperature, blood pressure, heart rate, respiratory rate, height and weight)
d) Physical complications of substance use (e.g., evidence of stigmata, abscesses, endocarditis or other infectious diseases)
e) Diagnosis of Opioid Dependence by DSM-IV criteria
f) Urine drug screening and other relevant laboratory tests ie. HIV, hepatitis screening including pre- and post-test counseling.

For HIV and Hepatitis screening the following protocol will be adopted:

At entry:

a) Participants will be tested for hepatitis A, B and C and HIV unless written confirmation of positive results is available.
b) Participants who test negative for hepatitis A and B will be offered vaccinations. For those participants who have already been vaccinated anti-HBsAg testing will be done and revaccination or boosters will be given as required.
c) Participants, who have tested HCV positive, will have liver function tests

At 6 months:

d) Participants who are negative at baseline will be tested for HIV and HCV
e) Participants who received Hep B vaccinations at baseline will be tested for anti-HBs and given booster doses.
f) Participants who did not receive Hep A & B vaccinations at baseline will be re-tested for hep A and B, and again offered vaccinations.
g) Participants, who have tested HCV positive, will have liver function tests

At 12 months:

h) Participants, who have previously tested negative, will be tested for HIV and HCV at each time point.
i) Participants, who have tested HCV positive, will have liver function tests

For female clients: BHCG. Both male and female clients will receive STD prevention education

16.5. Psychiatric Assessment

The initial psychiatric assessment will include the following:

a) Initial psychiatric screening to ensure no pre-existing severe mental disorders exist that are contraindicated for diacetylmorphine therapy; a treatment referral for more intensive psychiatric therapy will be issued to an independent facility if a contraindication exists.
b) Identification of less severe mental disorders which do not preclude participation in the study but which will be addressed as part of the treatment offered.
16.6.  Urine Toxicology

Urine samples will be collected to monitor compliance with the prescribed medication and to monitor use of other non-prescribed medications. Clients will be asked to leave urine samples according to provincial MMT guidelines. The results will be for clinical purposes. The research team will have access to the results of the urine tests done in the treatment clinic and those done in the research center; the clinicians will have access only to those done in the treatment clinic. Treatment urine specimens will be used to modify dosage levels and to increase doses where indicated. Research urine samples will be used to determine the use of illicit drugs outside of study medications as one of the study's outcome measures.

Collection Schedules:
› Samples intended for clinical use will be collected using a random schedule.
› Samples intended for research use will be collected using a fixed schedule

Collection Specifications:
› Use of temperature strips is thought to be less intrusive than supervision and is therefore preferred

Substances to be tested:
› Samples intended for clinical use will be analyzed using methodology currently available at the study site (as an example, if EMIT testing is used, the screen should include barbiturates, benzodiazepines, cocaine metabolite and opiates)
› Samples intended for research use, collected at each follow-up visit by the research office, will be analyzed for the presence of the following substances:
  - Illicit heroin use by detection of Papaverine and Noscapine metabolites and acetylcodeine;
  - Amphetamines, Benzodiazepines, Cocaine, Opioids, and Methadone Metabolite

Samples will not be routinely tested for tetra-hydro-cannabinol (THC) as it is felt that THC use is likely to be fairly common and often not associated with adverse consequences for the user. Where participants exhibit mood or anxiety symptoms, clinicians may request THC testing to assist their clinical history in determining the extent to which these symptoms are induced by THC use.

16.7.  Treatment compliance and rate of loss to follow-up

Treatment retention is expected to be extremely high based on observed data from NAOMI and we expect 85% of participants to remain in treatment throughout Stage I. Regarding stage II, it is not clear how many participants will accept the switch from injecting to oral medication after the second randomization. However this is part of the research question: Is it possible, after stabilizing a participant with injection medication, to switch them to treatment with an oral medication without loss of treatment benefit? Participants randomized in Stage II to oral medication who reject the switch, will
either transition to other treatments (for example methadone) or will leave treatment. If this occurs to a significant degree and leads to loss of clinical benefit, this will be reflected in the outcome evaluation of the oral group.

Despite the marginalized and transient nature of the study population, follow-up in NAOMI has been excellent. Participants visit a separate research office for their research follow-up visits and receive a stipend of $25 to $35 for each visit, whether or not they are retained in treatment at the clinic. The independence of the research office from the clinic together with an experienced research staff that has developed innovative ways of finding participants (e.g. visiting jails) has resulted in low rates of loss of follow-up evaluation for research purposes. In NAOMI, the loss to research follow-up rate in the injection arm at 12 months was less than 3%.

17.0 Efficacy Variables and Analysis

17.1. Primary Outcome Measures

The primary outcome measure (POM) for both Stages I and II will be illicit heroin use defined as the number of days of illicit (“street”) heroin in the prior 30 days of each end point by means of self-report. There is substantial evidence regarding the validity of self-report data collected from drug users in a research context. Darke reviewed the available literature investigating self-report and concluded that, when the information provided has no influence on future treatment or other potential impacts on the participant, the literature shows respectable reliability and validity of self-reported behaviours when compared to biomarkers, criminal records and collateral interviews. Indeed, most of the scales used in addiction treatment trials such as the ASI, the OTI and the SCL-90 are based on self-report.

17.2. Secondary Outcome Measures

Secondary outcome measures will include health status, treatment retention, use of additional methadone, cocaine use, urinalysis and criminal involvement (see below for descriptions of each measure). Adverse event documentation and reporting will be consistent with Good Clinical Practice (GCP) and Health Canada regulations. NAOMI has provided much experience in the latter regard, with over 110,000 injection treatment episodes. Two sub-studies are incorporated in this proposal: health economics evaluation and success of the blinding.

State of health

Physical health is defined as the number of symptoms according to the health scale of the Opioid Treatment Index (OTI). Mental health is based on the Global Severity Index GSI of the SCL-90-R.

Treatment Retention

Treatment retention will be defined as the time to discontinuation of SALOME treatment during the study treatment period and will be assessed using a combination of study clinic records (study medication), Pharmanet database (methadone and buprenorphine) and self-report (abstinence oriented treatments or treatment in other provinces).
Participants’ Satisfaction with treatment

We will assess participants’ satisfaction with treatment using the Client Satisfaction Questionnaire (CSQ)\(^{92}\). This is a brief 8-item questionnaire regarding satisfaction with the treatment as provided in this study, adding two open ended questions asking what the liked and disliked and their recommendations for improving the treatment. The baseline and 18 month and 24 month follow up evaluations will be modified to assess the treatments participants have received in the prior 30 days, and their satisfaction with these treatments.

Co-prescribed methadone

During the study, participants can add oral methadone to their treatment regimen or totally switch to MMT. The addition or complete switch to oral methadone will be evaluated in relation to the primary outcome and treatment retention.

Cocaine use

Following the process for evaluating illicit heroin use, cocaine use will be measured as number of days of use (self-report). Given the nature of cocaine metabolism in relation to opioids, cocaine can be taken several times a day. Thus, a modified version of the MAP, adding the number of times cocaine, in any form, as been taken will be evaluated. Also, addiction questionnaires such as ASI and MAP report either the main or the most risky route of administration. For this study we will consider each route separately, reporting all routes of administration.

Total illicit opioid use

The primary outcome of the study is illicit heroin use in the prior month. However, the inclusion criteria specify any illicit opioid use in the prior month. Some individuals might have access to other illicit opioids besides heroin, and occasionally use them such as illicit morphine. Based on NAOMI data, this is very rare. Nevertheless, the number of days using illicit heroin in the prior month might slightly underestimate total illicit opioid use, if participants used other illicit opioids on days they could not access heroin.

Toxicological analysis

It is possible to detect the metabolites of illicit heroin in patients receiving pharmaceutical diacetylmorphine due to the availability of several pharmacologic tests (acetylcodamine and noscapine) developed in the last years \(^{93-96}\). Several studies have reported on the agreement between self-report and urine or plasma indicators of illicit heroin. For example, Paterson \textit{et al.} \(^{97}\) reported that of the 37 participants reporting heroin use within the preceding 48 hours, morphine (a metabolite) was detected in 36 (97\%) cases, and papaverine metabolites were detected in 35 cases (95\%). Rook \textit{et al.} \(^{95}\) reported on the detection of acetylcodamine as a biomarker for illicit heroin among HAT patients, finding a high (93\%) percentage of agreement between self-reported illicit heroin use and the test result, and a Kappa score of 0.73.
Considering that daily urine sampling is unfeasible and heroin metabolites remain detectable for several days, urinalysis cannot be used to completely validate the self-reported number of days of illicit heroin in the POM. However it can be used to assess self-report use or non-use more generally. We will determine the proportion of positive urinalyses for illicit heroin in the scheduled follow-up visits. Testing for illicit heroin markers is performed at the Provincial Toxicology Centre. Testing for amphetamine, benzodiazepines, cocaine, methadone metabolite and opioids markers are performed by LifeLabs.

**Criminal involvement**

To evaluate the involvement in criminal activities during the trial we will use a combination of self-reported data (ASI and MAP questionnaires) and court house records. The recently published study on the criminal activity in the German HAT trial demonstrates the importance of combining self-report and institutional records when analyzing criminal activities in relation to addiction treatment.

17.3. **Health economics and quality of life measures**

SALOME will provide the first ever opportunity to conduct a full economic evaluation comparing HDM vs. DAM, both orally administered and injected, alongside an RCT. This will enable policymakers to assess the economic value of HDM when making resource allocation decisions.

The cost-effectiveness of the alternative treatment regimens in each stage will be assessed using two alternative economic evaluation study designs following standard methodology. We will first conduct a within trial cost-effectiveness analysis comparing HDM vs DAM over the time horizon of the trial. The EQ-5D, a measure of health related quality of life, will be measured to calculate the quality-adjusted life years (QALYs) gained for each patient using Canadian preference weights. Similarly, we will calculate the accumulated costs of opioid substitution treatment, drug treatments for HIV and hepatitis C virus infection, other healthcare use including hospitalizations and physician visits, self-reported criminal activity and criminal charges. Fully allocated treatment costs of HDM and DAM, including costs of medication, human resources and overhead, will be sourced from the study site. The data required to perform these analyses will be collected partly by a modified version of the EuropASI (with supplements). Thus, incremental cost-effectiveness ratios (ICER; the ratio of the difference in costs and the difference in QALYs between treatment arms) will be calculated for each treatment group. Guidelines for good practice in conducting economic evaluations alongside RCTs will be adhered to.

Our second design will modify a semi-Markov model, developed for the NAOMI economic evaluation, to inform policy makers of the cost-effectiveness of providing DAM vs. HDM vs. current standard care (MMT). As such, we will ultimately combine the SALOME data with the NAOMI trial data to facilitate this policy relevant question. The model will extrapolate trial-based results to project quality-adjusted life expectancy and lifetime costs for each treatment group by following a cohort of hypothetical patients through transitions of treatment, abstinence, relapse or death. Evidence for these short term transitions will come from both the SALOME and NAOMI trial - MMT will be estimated using an indirect regression analysis where HDM vs DAM and DAM vs MMT data is combined so the relative effect of HDM can be estimated. The short-term data will be combined with longitudinal data found in a review of the literature. Costs and QALYs for each health state will be sourced as previously. Both deterministic sensitivity analysis, evaluating the effects of altering individual model parameters on the ICER, and probabilistic sensitivity analysis varying all...
model parameters simultaneously to take into account the complete range of uncertainty in costs and effectiveness, will be conducted.

In each design, the societal perspective will be adopted, thus including the direct and indirect costs of treatment. In addition to the costs of medication, inpatient and outpatient care and the costs of criminal activity will also be incorporated. Costs of concurrent pharmacotherapies will be ascertained from linked data from the Pharmanet database, while costs of inpatient and outpatient care will be ascertained from linked data from the Medical Services Plan, Discharge Abstract Databases, Mental Health and MSP consolidation file, all available from Population data BC (see SALOME Informed Consent Form and Release of Information Form-10 ‘BCpopdatabase’). The costs of police, judicial, corrections and crime victimization will be calculated using information from the Canadian Centre for Justice Statistics. A ministry of health, and third party payer perspective will also be performed as a sensitivity analysis.

17.4. Success of the Blinding

Objectives

The general aim of this sub-study is to test the success of the double-blinding of hydromorphone and diacetylmorphine in the SALOME study. The specific aims of the testing of the blinding are:

a) To determine what drug that participants think they received;

b) To determine what drug health care providers, outcome assessors and statisticians think participants received;

c) To examine the association of what drug participants think they received with their treatment allocation expectations, previous experience with hydromorphone, subjective drug perceptions (e.g., high, flash), treatment outcomes (i.e., illicit opioids use) and drug side effects (e.g., drowsiness);

d) To investigate the association of what drug health care providers, outcome assessors and statisticians think participants received with the treatment outcomes (i.e., illicit opioids use) and drug side effects.

Methods and Design

The method to test the success of blinding in the SALOME trial will follow best practices and current recommendations for assessing blinding in randomized controlled trials. These recommendations highlight that a blinding assessment should not interfere, bias or jeopardize the assessment of the treatment effectiveness. Therefore, this sub-study is designed in a way that will allow determining if the participants were taking hydromorphone for diacetylmorphine without introducing any confounder variable that could jeopardize the treatment effect and evaluation of the primary outcome of the SALOME trial.

In the SALOME trial, only the pharmacists will know if the medication participants’ are receiving is hydromorphone or diacetylmorphine; participants, clinical and research team will be blinded for the formulation, however not for the route of administration (phase II). The research team, which is independent of the clinical team, will conduct the evaluations aimed at testing the blinding. The assessments for this sub-study will be carried out in the same format and setting as the SALOME study research evaluations. Few assessments must be taken at the clinic (blinding success after titration; health care providers’ perception of treatment). The research office will coordinate with the study clinic to perform these evaluations with minimal impact for the operation of the clinic.
It has been suggested that health care providers and research team ‘hunches’ regarding the blinding might influence participants’ ‘guesses’ of the medication they are receiving. Thus, in SALOME, participants, health care providers, outcome assessors (interviewers) and data analysts will participate in the testing of the blinding. The success of the blinding will be tested through a combination of standardized instruments, observations, and questions (some of them are part of the SALOME research instruments) obtained at various study points.

Data Collection

Data for testing the success of the blinding will be gathered during screening, before randomization, after drug titration and at 3, 6, 9, 12, 18 and 24 months (Table 3 shows the time-line and details of the data collection).

It has been proposed that participants’ perception of the blinding changes during the course of a study and more than one assessment are needed in order to capture these potential fluctuations. However, studies suggest that a two-point model of assessment is the indicated one, since no significant differences have been found with a six-point model of assessment. This is of highly importance given of the serious concerns of causing additional unblinding and report bias due to drawing attention to the ‘blinding issue’ with repeated questioning around the topic.

What drug participants think they received will be assessed at the beginning and at the end of their treatments in each study phase (see Table 3). The first assessment will be early in the first weeks of the study (after titration), in an attempt of gathering these answers before patients and health care providers have constructed their perception about the effectiveness of the treatment. Those randomized to the oral route of administration in the second phase will be assessed again in the first weeks (after titration) after treatment allocation. The perception of the blinding will be again assessed at the end of each study phase, after collecting the end-point data (however in the same session). The assessment, early in the study, will be done with great caution to avoid make participants ‘guessing’ the treatment or ‘curious’ about what they are receiving. In order to do so, questions regarding the blinding will be interspersed along different sections of the SALOME study interview.

A similar timing and questions format will be applied to gather data from health care providers, outcome assessors and data analysts regarding the success of blinding. Data analysts will be asked what drug they think participants received after the first set of data and at the end of the study. Questions about subjective drug effects before and after participants take the medication are asked by a peer worker, to facilitate the data collection. The peer worker also collects the health care providers’ perception of treatment and general treatment effectiveness.

Assessments tools

Treatment allocation expectations: Questions regarding participant’s treatment choice or preferences will be asked in order to evaluate how much their expectations can influence their response of what drug they think they are receiving. Participants will be also asked if they think they can recognize hydromorphone, to assess believes of their abilities towards unmasking the treatment. During screening, when participants do not know yet if they will be eligible for the SALOME study, the following questions will be placed: a) If all of these treatments were available and you could choose to enrol in them, what would your preferences be? Heroin, injectable/oral, Dilaudid, injectable/oral.
(never/not sure/may be/definitively); b) If only (injectable/oral) Dilaudid® was available, in addition to what is available in the community (e.g., MMT), would you start this treatment Yes/No/Not sure; c) If you do not know what is in a syringe/drink, do you think you would know if you are injecting/drinking heroin or Dilaudid®? Yes/No/Not sure. Questions a and b will be asked again at the end of both study phases and at 18 and 24 months follow-up, after evaluation of treatment effectiveness to assess change over time.

We will also place the following questions at screening: a) What drug would you wish to get in phase I? Injectable Heroin/not sure/Injectable Dilaudid®; b) What route of administration would you wish to get in phase II? Injectable/Not Sure/Oral; c) If you are switched to oral what drug would you wish to be receiving in phase II? Oral Heroin/Oral Dilaudid®/Neither/Not sure. These questions differ from the previous one (‘...if you could choose...’) in the fact that the emphasis here is in the ‘hope’ of the randomization outcome, and the former is intended to build a scenario where the participant could make a choice (possibility if treatments available). Questions b and c will be repeated prior to phase II randomization.

NAOMI participants: To have been participated in NAOMI is not an exclusion criterion to participate in SALOME. It is very unlikely that some NAOMI participants could recognize the drugs because they have had experience already with medically prescribed injectable hydromorphone or diacetylmorphine. NAOMI participants, at baseline, indicated they have used street hydromorphone and heroin, although they did not guessed the treatment. Moreover, they were never disclosed the drug they received, and they stopped receiving the injectable medications several years ago (between July 2006 and July 2008). Therefore, we see no reason to deny NAOMI participants to apply for SALOME, and an ethical concern arises if we intend to do so under the assumption of possible unblinding. Nevertheless, we will control this variable and former NAOMI participants will be flagged in the database and their randomization code in the former study will be added (oral methadone, injectable diacetylmorphine or injectable hydromorphone). Also, during screening, former NAOMI participants will be asked what drug they thought they received during NAOMI.

Previous experience with hydromorphone: Before randomization, participants will be asked about their previous use of hydromorphone, including questions such as age of first use, regular use, route of administration and use in the prior month.

Treatment assignment: Participants will be asked to guess treatment assignment, allowing them to express uncertainty and answer “do not know” or “not sure”. Street name of diacetylmorphine and hydromorphone will be used: Which drug do you think you received? 1) Heroin definitely; 2) Heroin possibly; 3) not sure; 4) Dilaudid® possible; 5) Dilaudid® definitely (this is the same format used for NAOMI).

Reasons for treatment assignment response: At the end of the study, participants, health care providers, outcome assessors and data analysts will be asked why they think participants received one drug or the other, or were unsure. These will be qualitative questions: ‘Why do you believe you were on treatment x?’ ‘When did you come to that conclusion?’ In order to avoid to make participants try to guess even in their future trials, these questions will be asked together with other general questions (e.g., participants’ satisfaction, problems or other comments) at the study close-out.

Route of administration: Participants’ route of administration of illicit use of opioids will be assessed using the EuropASI format, differentiating between intravenous, intramuscular and subcutaneous.

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2 We do not include other opioid maintenance treatments in this question, since our target population are individuals not benefiting sufficiently from mainly methadone. We believe methadone would be negatively perceived in comparison with the study treatments, providing a biased response.
previous pilot study (see background section) found injectable opioids subjective perception varied depending on being used intravenously, intramuscularly or subcutaneously. Therefore, participants will be asked how frequently they used those routes of administration with the study medications prescribed at the clinic.

**Drug effects:** Participants’ self-reports of drug effects will be assessed with a modified version of an adjective rating scale (ARS)\(^{106}\) and with a visual analog scale (VAS)\(^{59}\). The ARS is a standardized measure listing 37 items describing opioid drug effects and withdrawal effects. Participants rate the degree to which they had experienced each symptom during the past 24 hours on a scale of 0 (not at all) to 4 (extremely) and after drug administration. Example of questions for opioid effects include items such as ‘sleepiness’ and ‘skin itchy’, while withdrawal effects include such items as ‘sweating’ and ‘yawning.’ In the VAS, participants rate the extent to which they had experienced six drug effects: Drug Effect, Drug Liking, Good Effect, Bad Effect, Drug-related High and Sick. Each item is rated from "not at all" to "extremely" with corresponding scores from 0 to 100.

**Adverse Events:** Data on Adverse Events will be collected as part of the SALOME protocol (see 18.0)

**Treatment effectiveness appraisal:** It is expected that study participants will begin early to create a perception regarding the treatment benefits and if it is or it is not working for them. For these reasons, it has been suggested that we might not be testing for blindness, but for ‘hunches’ about effectiveness\(^{64}\). Thus, when participants have done well, they may tend (as well as health care providers) to predict they were on the desired medication (regardless of treatment allocation). In order to control this variable, participants and health care providers will be asked if they think the treatment is effective for each particular participant with three options: yes, no, not sure.

A question about treatment effectiveness in general will be asked to health care providers, outcome assessors and data analysts regarding hydromorphone and diacetylmorphine, injectable and oral: Do you think that hydromorphone/diacetylmorphine, injectable/oral is an effective treatment for long-term opioid-dependency? Answers will be Yes/No/Not sure. This question is aimed at evaluating treatment effectiveness beliefs for the drug and route of administration beyond the perceived participants individual treatment outcomes.

### Table 3: Research Time Points and Planned Data Collection for assessing success of the blinding

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<tr>
<td>Study treatment assignment guess</td>
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<td></td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
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<table>
<thead>
<tr>
<th><strong>ARS</strong></th>
<th>Treatment effectiveness appraisal</th>
<th>Study treatment assignment guess</th>
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<td>Treatment effectiveness appraisal</td>
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**Health Care Providers**

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<tr>
<th><strong>Other Staff</strong></th>
<th>Treatment assignment, outcome assessors</th>
<th>Treatment assignment, statistician&lt;sup&gt;(b)&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Study treatment assignment guess</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>General treatment effectiveness appraisal</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Participant treatment effectiveness appraisal</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Treatment assignment, statistician<sup>(b)</sup>

ARS= Adjective Rating Scale; VAS=Visual Analog Scale

(a) Only to those allocated to oral route of administration

(b) When analyzing data.

### 18.0 Safety Variables and Analysis

#### 18.1. Definitions According to ICH E2 Section II

An adverse event is defined as any untoward medical occurrence in a participant administered a pharmaceutical product which does not necessarily have to have causal relationship with the treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product.

This includes:
- an event not present prior to drug administration;
- discovery of undiagnosed pre-existing condition after drug administration;
- exacerbation of pre-existing condition;
- increased frequency of an intermittent event;
- any change or worsening.

This does not include:
- continuous, pre-existing condition which does not change in nature or intensity;
- treatment failure.

A serious adverse event (SAE) is any adverse drug experience or adverse event occurring at any dose that:
- results in death;
- is life-threatening;
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect;
- important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the above outcomes.

Adverse Drug Reaction (ADR) in the pre-clinical experience with a new medicinal product or its new usages, is all noxious and unintended responses to a medicinal product related to any dose.

18.2. Classification of Events

Relationship

Many terms and scales are in use to describe the degree of causality (attributability) between a medicinal product and an event, such as certainly, definitely, probably, possibly or likely related or not related. Phrases such as "plausible relationship," "suspected causality," or "causal relationship cannot be ruled out" are also invoked to describe cause and effect. However, there is currently no standard international nomenclature. The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

The following terms describing relationship will be used in the SALOME study:

**Not Related:** Where a temporal (timely) relationship of the onset of the event, relative to the administration of the product is not reasonable. E.g. cut finger. Or where another cause can explain the occurrence of the event by itself E.g. Headache associated with Migraine.

**Unlikely:** Where a temporal (timely) relationship of the onset of the event, relative to the administration of the product is unlikely but cannot be ruled out. E.g. mouth ulcer following admin of oral drug.

**Possibly Related:** Where a temporal (timely) relationship of the onset of the event, relative to the administration of the product is reasonable, but the event could have been due to an equally likely cause. E.g. Headache.

**Probably Related:** Where a temporal (timely) relationship of the onset of the event, relative to the administration of the product is reasonable and the event is more likely to be explained by the medicinal product than by another cause. E.g. nausea and vomiting.

**Definitely Related:** Where a temporal (timely) relationship of the onset of the event, relative to the administration of the product is reasonable and there is no other cause to explain the event (or a rechallenge is positive) E.g. Overdose.

Out of these five categories, “possibly”, “probably” and “definitely” related to a medicinal product qualify as adverse reactions. “Unlikely” and “not related” do not qualify as a reasonable causal relationship.

Severity

AEs and SAEs will be classified according to severity.
- Mild = hardly noticeable, negligible impairment of well-being (minor itch)
- Moderate = marked discomfort, but tolerable without immediate relief, interferes with normal activities (e.g. excessive sedation)
- Severe = overwhelming discomfort, calling for immediate relief (e.g. Overdose)

Severe does not equal Serious, unless the event meets the criteria of a SAE

**Expectedness**

*Expectedness of an Adverse Drug Reaction*

The purpose of expedited reporting is to make regulators, investigators, and other appropriate people aware of new, important information on serious reactions. Therefore, such reporting will generally involve events previously unobserved or undocumented, and a guideline is needed on how to define an event as "unexpected" or "expected" (expected/unexpected from the perspective of Clinical Safety Data Management previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product).

As stated in the definition, an "unexpected" adverse reaction is one, the nature or severity of which is not consistent with information in the relevant source document(s). Until source documents are amended, expedited reporting is required for additional occurrences of the reaction. The following documents or circumstances will be used to determine whether an adverse event/reaction is expected:

1. For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as the source document in that country. See ICH Guidelines
2. Reports, which add significant information on specificity or severity of a known, already documented serious ADR, constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected".

**18.3. Data Collection Procedures for Adverse Events and Serious Adverse Events**

*Background Noise*

Per ICH GCP E9 6.0 “In situations when there is a substantial background noise of signs and symptoms (e.g. in psychiatric trials) one should consider ways of accounting for this in the estimation of risk for different adverse events. *One such method is to make use of the "treatment emergent" (see Glossary) concept in which adverse events are recorded only if they emerge or worsen relative to pretreatment baseline.*

Other methods to reduce the effect of the background noise may also be appropriate such as ignoring adverse events of mild severity or requiring that an event should have been observed at repeated visits
to qualify for inclusion in the numerator. Such methods should be explained and justified in the protocol.”

In order to reduce the effect of background noise in SALOME, the following common adverse events, when occurring MILD in severity, will not be collected: Withdrawal, Drowsiness/sedation, Histamine Reaction, Constipation, Insomnia, Headache, Superficial abrasions.

Pre-existing conditions/symptoms will not be collected as adverse events unless the condition/symptom worsens.

**Time Frame for AE Capture**

Adverse events will to be captured from time of randomization to 30 days after study drug treatment is completed. All unresolved AE's will be followed until resolution, 30 days after study treatment ends or subject is lost to follow-up, whichever comes first.

Serious Adverse Events will be captured and followed from time of randomization to 30 days after study treatment ends, resolution or subject is lost to follow-up, whichever comes first.

**Collection of Adverse Events and Serious Adverse Events**

All study participants will be assessed for adverse events (AEs), drug reactions or changes in health status during all visits to the clinic by clinic nurses, coordinators, physicians and/or other clinic workers. All possible AEs and SAEs will be documented in the CRF at the clinic. Information to be documented includes date and time of last dose of study medication, administered dose, description of event and date, time and duration of the event, details of any treatment administered, concomitant medications, laboratory test results and relationship. Follow-up information should be sent in a timely manner until event is resolved. The research office will report possible SAEs (mainly hospitalizations) among participants not retained or not compliant with the doctor appointments. Once an SAE is confirmed by the Clinical Trial Coordinator, it will be added to the CRF.

SAEs must be reported to the Clinical Trial Coordinator within 48 hours once the site is aware of the event.

18.4. **Reporting SAEs and Unexpected AEs**

**Single Cases of Serious, Unexpected ADRs**

All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting. This applies to reports from spontaneous sources and from any type of clinical or epidemiological investigation, independent of design or purpose. It also applies to cases not reported directly to a sponsor or manufacturer (for example, those found in regulatory authority-generated ADR registries or in publications). The source of a report (investigation, spontaneous, other) will always be specified.
Causality assessment is required for clinical investigation cases. All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs. For purposes of reporting, adverse event reports associated with marketed drugs (spontaneous reports) usually imply causality.

All SAEs considered unexpected and related to study treatment are to be reported to Health Canada as well as the local ethics committee. Following appropriate clinical intervention and/or implementation of appropriate emergency protocols, the “SAE Report Form” is to be completed and submitted to the Clinical Trial Coordinator who will ensure that systematic and standard procedures for registration, notification and follow-up are followed.

**Time Frame for Reporting**

**Fatal or Life-Threatening Unexpected ADRs**

Fatal or life-threatening, unexpected ADRs occurring in clinical investigations qualify for very rapid reporting. Regulatory agencies will be notified (e.g., by telephone, facsimile transmission, or in writing) as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible within 8 additional calendar days.

**All Other Serious, Unexpected ADRs**

Serious, unexpected reactions (ADRs) that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.

19.0 Data handling and quality assurance

Data will be handled at the Centre for Health Evaluation and Outcome Sciences at St Paul’s Hospital in Vancouver. Data will be transferred electronically using password protected files that the Research Staff, Principal and Co-Investigators, Statistician and Data Manager will have access to. All paper and electronic data will be stored in locked filing cabinets and/or password-protected computer files on a secure server at the St Paul’s site. Information from the research offices will be kept in a locked filing cabinet at each site and data will be transferred to the St Paul's site periodically.

Quality control is ensured in a variety of ways. First, study protocols will be reviewed and approved by the steering committee. Intake, participant selection, randomization, and evaluation procedures will be recorded in an operations manual and updated periodically based on changes approved by members of the steering committee, according to expertise and roles in the study.

Interviewers and other clinic staff will receive consistent and extensive training prior to the start of the study. Reliability and validity studies (e.g., repeat urinalysis) will be conducted. Site visits by members of the steering committee will be done on a semi-annual basis to ensure protocols and data collection are followed.

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Quality of data entry will monitored through routine audits at the data centre for accuracy and reliability. All data forms will be visually inspected by a data manager and double-entered into an ORACLE database. Checks for inconsistencies and missing data will be performed routinely, and the data coordinator will send out queries to the participating sites to clarify possible errors. All major changes in data processes will be approved by the steering committee to maintain the integrity of the protocol.

20.0 Statistical Analysis

The planned analysis is based on the non-inferiority nature of the comparisons in both stages. The primary outcome measure (POM) for both Stages I and II will be number of days of illicit heroin use as defined in Section 17.1. Non-inferiority will be evaluated by examining the 90% confidence interval, one sided $\alpha=0.05$, around the difference between HDM and DAM in Stage I, and around the difference between injection and oral medications in Stage II. If the lower bound of the confidence interval excludes the margin (4 days), non-inferiority will be established. Because of the non-inferiority design of the trial, the analysis of outcome at 6-months and at 12-months will be conducted both on an intent-to-treat (ITT) and per-protocol basis. We expect no more than 4% loss-to-research follow-up in each phase. We will analyze the participants who are lost-to-follow-up using the multiple imputation technique in order to fully understand the uncertainty due to missing data.

It is possible that illicit heroin in the prior 30 days is not normally distributed. In that case, this variable will be dichotomized, defining success as 3 days or less of illicit heroin use in the prior month. The non-inferiority margin of 4 days translates to a relative effect size of 0.80. If the lower bound of the confidence interval excludes the margin defined as 0.8 multiplied by the success rate of DAM in stage I and injection in stage II, non-inferiority will be demonstrated.

No interim analyses are planned. Stage I will be analysed once all Stage I participants have completed the 6-month primary outcome assessment. Once half of the patients have completed Stage I, an analysis of retention in injection medication will be conducted. This will be used to adjust the number of participant recruited into Stage I to ensure a sufficient sample size in Stage II.

No subgroup analyses are planned.

Blinding Success: Due to the ‘wishful thinking’ (participants want to receive diacetylmorphine, ergo, they think they received that drug), we expect a high rate of correct guessing in the diacetylmorphine arm and high rate of incorrect guessing in the hydromorphone arm. Data analysis will be performed under that premise. Blinding data will be described by treatment arm and role (study participants, health care providers, outcome assessors, data analyst). The success of the blinding will be analyzed using currently available blinding indexes. Inter-group comparison of the change in beliefs in the treatment received (and not necessarily if the believes were correct) between the start and end of a trial will be tested. Descriptive analyses will be performed for frequencies and means values for variables described in the success of the blinding sub-study section. Comparisons between variables will be carried out using Student’s $t$, Mann-Whitney U and Kruskal–Wallis tests for comparisons of means and Chi Square tests for comparisons of frequencies, depending on variable distribution. For example, number of adverse events, type and relation to treatment will be compared for each treatment arm.
looking for associations with success of the blinding assessments. Data will be carefully interpreted, specially the association of the blinding success with treatment efficacy results. If significant unblinding occurred in the hydromorphone arm, we will be testing for the bias-generating consequences of the loss of the blinding, specifically regarding treatment effect and adverse events.
References


64. Sackett DL. Commentary: Measuring the success of blinding in RCTs: don't, must, can't or needn't? *Int J Epidemiol* 2007; 36(3): 664-5.


