Working Paper

Evidence on the Effectiveness of Heroin-Assisted Treatment

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Preface

Current levels of opioid-related morbidity and mortality in the United States are staggering. Data for 2017 indicate that there were more than 47,000 opioid-involved overdose deaths (roughly similar to deaths from AIDS at its peak in 1995), and 1 in 8 adults now report having had a family member or close friend die from opioids. There has been a near universal call from blue-ribbon commissions and expert panels for increasing access to Food and Drug Administration-approved medications for those with an opioid use disorder; however, jurisdictions addressing opioid use disorders and overdose may wish to consider additional interventions beyond increasing access to these medications. Two interventions that are implemented in some other countries but not in the United States are heroin-assisted treatment (HAT) and supervised consumption sites (SCSs). Given the severity of the opioid crisis, there is urgency to evaluate tools that might reduce its impact and save lives.

This working paper is part of a series of reports assessing the evidence on and arguments made about HAT and SCSs and examining some of the issues associated with implementing them in the United States. The target audiences include decision makers in rural and urban areas grappling with opioids as well as researchers and journalists. This document is a review of the HAT literature. The other parts of this series of reports include: (1) a summary report of all the components of the research study; (2) a review of the SCS literature; (3) a report on key informant views on the acceptability and feasibility of implementing HAT and SCSs in selected U.S. jurisdictions heavily affected by the opioid crisis and (4) a report on international experience with the implementation of HAT and SCSs.

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Summary

With the dramatic rise in overdose mortality related to heroin and synthetic opioids, there has been increased attention to the role of innovative strategies to expand access to treatments for opioid use disorder in order to combat the rising social costs of the opioid crisis. As a treatment option for individuals with chronic heroin dependence who have not responded to traditional medication therapies, several countries have experimented with offering pharmaceutical-grade heroin as treatment for opioid use disorder. Today, heroin-assisted treatment (HAT) is available in 58 clinics across eight countries, with four countries offering HAT as part of the standard treatment system. This study assesses evidence for the effectiveness of HAT with respect to individual, community, and economic outcomes.

To identify existing research, we searched five electronic databases for peer-reviewed articles and "grey literature" reports published between January 1990 and January 17, 2018. For patient-level outcomes, we provide an overview of the current evidence base from existing systematic reviews and recent randomized controlled trial (RCT) results as well as a narrative discussion of individual RCTs. For community-level and economic outcomes, we also considered non-RCT study designs.

Key insights from the review:

- **Patient-level outcomes**: Evidence from the ten RCTs reviewed indicates that supervised injectable HAT with optional oral methadone can offer benefits over oral methadone alone for treating opioid use disorder (OUD) among individuals who have tried traditional treatment modalities, including methadone, multiple times but are still injecting heroin. The strongest and most consistent effects across studies are shown for reducing illicit heroin use and improving treatment retention. These are important findings given the current harms people who use heroin face from exposure to fentanyl and other synthetic opioid in many illicit markets. However, one reason HAT treatment retention rates were higher than methadone treatment retention rates is that some participants randomly assigned to oral methadone immediately dropped out of treatment. Another is an asymmetry caused by defining retention as remaining in any treatment; HAT participants can (and do) switch to methadone, but the converse was not permitted in the trials.

  There is also suggestive evidence that, within these populations, HAT may be more effective than oral methadone in reducing individuals' criminal activity and illicit use of benzodiazepines, as well as for improving their physical and mental health. But there is strong evidence indicating that HAT carries significantly greater risk than oral methadone for serious adverse events. Thus, the relative benefits of HAT versus oral methadone for some patients must be balanced with the risks associated with it.

- **Community-level outcomes**: We identified five studies that evaluated how HAT related to community-level outcomes. All studies employed a pre-post design or provided descriptive evidence based on participant incidents within a heroin-assisted RCT, with no study including a comparison group. Given the small number of contexts studied, methodological limitations with the research designs, differences in how community-level outcomes were measured, and the imprecision of estimated effects from the studies, we find the evidence for HAT's effect on community-level outcomes to be inconclusive.

- **Economic outcomes:** Although HAT is more expensive than oral methadone, HAT may be more cost-beneficial for clients who are refractory to standard treatments, largely through HAT's effect on reducing criminal activity among its target population. In the United States, methadone is only supplied as an oral medication. Supervised injectable HAT is much more expensive to administer than oral methadone mainly because of the staffing requirements associated with the supervision of injections, but it may still offer a better societal benefit-cost ratio for those who have previously undergone treatment but were still using heroin. This is primarily because evaluations in the literature credit HAT with doing more to reduce participants' levels of criminal involvement. Most trials also showed that users in the HAT arm enjoyed higher quality-adjusted life years (QALYs) relative to those who were assigned to oral methadone. However, that distinction may come from the greater supervision or the mode of administration rather than the chemical; among the two studies comparing the cost-effectiveness of supervised injectable heroin to other supervised injectable medications (methadone or hydromorphone), there were no significant differences between treatments in terms of costs or QALYs.

These findings are largely based on a review of the results of ten RCTs that have been implemented across seven countries (six European nations and Canada) and involved nearly four decades of investigation. While the RCTs have varied somewhat in how both the experimental and control conditions have been implemented, our summary findings are largely reflective of comparisons between supervised injectable heroin treatment (plus optional oral methadone) and oral methadone treatment. Importantly, given participant eligibility requirements, the evidence base reviewed should also largely be interpreted as one that informs the comparative effectiveness of HAT for treatment of heroin use disorder among a patient population that has previously attempted but not responded to oral methadone treatment. Findings are thus not intended to provide evidence regarding the use of HAT as a first-line treatment option. These conclusions also may not generalize to the effectiveness of HAT delivered through other routes of administration (e.g., oral heroin); or to comparisons of supervised injectable heroin with other medication treatments (e.g., buprenorphine). Indeed, evidence from a recent double-blind trial on the noninferiority of supervised injectable hydromorphone (e.g., Dilaudid) compared to supervised injectable heroin suggests additional opportunities for investigating innovative

treatments for heroin use disorder among patients who have tried and not responded to conventional first-line treatment options such as oral methadone.

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Abbreviations

ASI	Addiction Severity Scale Index
CHF	Swiss francs
HAT	heroin-assisted treatment
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
ITT	intent-to-treat
MSQoL	Modular System for Quality of Life
NAOMI	North American Opiate Medication Initiative
NICE	National Institute for Health and Care Excellence
NSDUH	National Surveys on Drug Use and Health
OUD	Opioid Use Disorder
PROVE	Medical Prescription of Narcotics Programme
QALY	quality adjusted life year
RIOTT	Randomized Injectable Opioid Treatment Trial
RCT	randomized controlled trials
SAE	serious adverse event
SALOME	Study to Assess Longer-term Opioid Medication
SCS	supervised consumption site

1. Introduction

Opioid use disorders, which in 2015 were estimated to have affected nearly 16 million people worldwide (Schuckit, 2016), contribute to risk of overdose death, promote risky behaviors, and complicate treatment for HIV and other co-morbid conditions (Becker et al., 2008; Broz and Ouellet, 2008; Estrada, 2005; Johnson et al., 2013; Kester et al., 2017). While much of the increasing trend in opioid use disorders over the past decade has been driven by rising rates of prescription opioid misuse, as of 2016, heroin use still accounted for about 76% of new opioid-related treatment admissions in the United States (SAMSHA 2018)[1] and, as of 2015, for about 80% of new opioid-related treatment demands in Europe (European Monitoring Centre for Drugs and Drug Addiction, 2017). Since 2010, the United States and Canada have experienced sharp increases in overdose rates involving heroin and, more recently, synthetic opioids such as fentanyl (Gomes et al., 2018; Rudd et al., 2016). Given the rapid escalation and continued evolution of the current opioid crisis, there has been increased effort to improve access to effective treatments (National Academies of Sciences Engineering and Medicine, 2017).

While the availability of medication treatment has increased substantially over the past decade, significant and persistent gaps have been well-documented, particularly in the U.S. context (Feder et al., 2017; Hadland et al., 2017; Jones et al., 2015; Morgan et al., 2018; Romo et al., 2018; Saloner and Karthikeyan, 2015). Estimates using 2012 U.S. data place the gap between treatment need and treatment capacity at nearly one million persons out of an estimated 2.3 million individuals with past-year opioid abuse or dependence (Jones et al., 2015), with evidence suggesting more pronounced disparities in rural and socioeconomically disadvantaged counties (Stein et al., 2018). Among individuals with opioid use disorder in the U.S., treatment utilization rates are low, with approximately 23 percent reporting past-year use of any drug use treatment service and less than 20 percent reporting use of opioid-specific treatment (Wu et al., 2016).[2] Estimates suggest only eight percent of opioid-dependent individuals worldwide receive medication treatment (Mathers et al., 2010; Vogel et al., 2017). The barriers to increased uptake of pharmacotherapies for opioid use disorder are multi-tiered and occur at the system, provider, community, and patient level (Oliva et al., 2011).

Methadone, a full opioid agonist, is the most studied pharmacotherapy for opioid use disorder (Sharma et al., 2017). Oral liquid methadone, administered in regulated clinics, has been a leading medication treatment for opioid dependence in the United States since the early 1970s. As a full opioid agonist, methadone has a high affinity for opioid receptors, i.e., methadone

[1] Data from publicly-funded treatment facilities.

[2] Based on 2013-2015 data from the National Surveys on Drug Use and Health (NSDUH).

competes with other opioids to activate the (primarily mu) opioid receptors. A large advantage of methadone to heroin and other illicit opioids is its long duration of action or half-life. A single "adequate" dose will activate opioid receptors for a full day or more – versus a few hours of activation by heroin. This allows users to stabilize over time – and fits well into a daily medication treatment regimen. Methadone is an effective substitute for other opioids in that it requires only once daily dosing and builds opioid receptor tolerance; however, because it is a full opioid agonist, withdrawal from methadone can be very difficult, and the possibility of overdose is always a consideration.

In the last 35 years additional medications, such as buprenorphine and naltrexone, have been approved to treat opioid use disorder. Buprenorphine is a partial opioid agonist that can be prescribed and dispensed much like any other medication without the need for a patient to frequent a specialized treatment clinic, as required for those taking methadone. In the U.S., buprenorphine can be prescribed by medical professionals (physicians, nurse practitioners, physician assistants) who undergo a specialty training to become a waivered provider. As a partial opioid agonist with a high affinity for the opioid receptor, buprenorphine has an advantage over methadone in that it alone will not activate opioid receptors to the point of toxicity or overdose, but it can still effectively compete with other opioids and block their agonist effects. Buprenorphine, like methadone, also has the advantage of a long half-life, allowing for longer periods between dosing, and for patients to achieve a degree of stabilization in their lives. In contrast, naltrexone is an antagonist that blocks the effects that opioids have in the body and is typically offered as a long-term injection to ensure abstinence and prevent relapse. Naltrexone has no potential for abuse or diversion, and thus faces limited regulatory barriers relative to buprenorphine or methadone (e.g., any health care provider licensed to prescribe medications can prescribe naltrexone). However, initiation of naltrexone requires full detoxification from opioids (typically seven to ten days of abstinence from opioids), including from methadone and buprenorphine. Combined with the relatively higher costs of naltrexone, the requirement to be opioid-free prior to induction may limit its feasibility for many individuals (Aletraris et al., 2015; Lee et al., 2018).

All three medication therapies (see **Table 1** for details) seek to reduce risk of relapse often associated with opioid use disorder, and the effects of these medications have been proven in clinical and real-world settings and are considered standard treatment (Veilleux et al., 2010; Volkow et al., 2014).

Table 1. Comparison of Medications for the Treatment of Opioid Use Disorder

	Methadone	Buprenorphine	Naltrexone
Example brand names	Methadose, Dolophine	Suboxone, Subutex, Zubsolv	Vivitrol, ReVia, Depade
Pharmacology	Full opioid agonist	Partial opioid agonist	Full opioid antagonist
More common modes of	Taken orally	Taken orally or sublingually[a]	Taken orally or as an

administration			intramuscular injection
Approximate dosing schedule	Daily	Daily (higher doses can be less-than-daily)	Daily for oral formulation or monthly for injection
Treatment setting	Specialty licensed opioid treatment program (OTP)	Certified physicians, nurse practitioners, and physician assistants can prescribe in office setting; OTP	Physicians, nurse practitioners, or physician assistants prescribe or order administration by qualified healthcare professionals
Advantages	High strength and efficacy in reducing opioid cravings and withdrawal symptoms if oral dosing is adhered to	Does not require visiting a specialized treatment clinic; lower risk of overdose than methadone	Not addictive or sedating and does not lead to physical dependence; monthly dosing schedule for injectable; lower regulatory barriers
Limitations	Only provided in separate system outside primary care may pose a barrier; stigma; risk of respiratory depression and cardiac rhythm disorder; linked to abnormalities in glucose metabolism	In outpatient setting, can only be prescribed by providers who obtain a federal "waiver," which may limit access; some abuse liability, though less with buprenorphine-naloxone combination formulations (e.g., Suboxone); induction involves mild-moderate withdrawal	Initiation requires at least 7 days of abstinence from opioids; poor patient compliance with oral form; logistical barriers to order or maintain injectable form; high overdose death risk due to self-discontinuation and hypersensitized opioid receptors; higher cost

Notes and sources: Adapted from the National Academies of Sciences Engineering and Medicine (2017); Sharma et al. (2017); and the American Society of Addiction Medicine (2015).
[a]A subdermal implant version of buprenorphine with a 6-month duration of action was recently approved by the U.S. Food and Drug Administration.

Nonetheless, not all patients are successfully recruited or retained in these medication therapies, and research has indicated that individuals with heroin use disorder – most of whom inject heroin – may face particular challenges in terms of treatment retention and treatment outcomes, in part due to higher rates of co-occurring mental and physical health problems, unemployment, and history of interaction with the criminal justice system (Bart, 2012; Cousins et al., 2016; Krebs et al., 2017; Moore et al., 2007; Wu et al., 2011). For agonist therapies in particular, potential barriers to participation are varied, including negative beliefs about agonist treatments; withdrawal symptoms and unwanted side effects such as nausea, headache, obstipation, and drowsiness; treatment costs; dosing and delivery characteristics; lack of fidelity to proper implementation practices; issues with the route of administration; and lack of euphoria (Fischer et al., 2002a; Fischer et al., 2002b; Peterson et al., 2010; Soyka et al., 2008; Uebelacker et al., 2016). Some may continue to consume heroin in addition to methadone or buprenorphine (Weiss et al., 2015), though use of other sedatives (e.g., alcohol, sleeping aids, and benzodiazepines) and illicit drugs (e.g., cocaine, methamphetamine, or phencyclidine) during treatment pose greatest threat in the form of overdose or dropout from treatment. As an antagonist, naltrexone is more limited in its application, primarily appropriate for patients who

have completed detoxification or have achieved abstinence during a period or incarceration or inpatient treatment and are at risk of relapse (Krupitsky et al., 2011; Lee et al., 2016; Nunes et al., 2018). Combined with the medication's relatively high costs (Jackson et al., 2015), pre-treatment abstinence requirements may explain why injectable extended-release naltrexone still comprises a small share of the overall treatment landscape for opioid use disorder (Morgan et al., 2018). Overall, though many have benefitted from standard treatment modalities for opioid use disorder, a subset of patients do not respond positively and continue to consume illicit opioids from street markets. These individuals may contribute disproportionately to the health and societal costs associated with heroin dependence (Fischer et al., 2007; Jiang et al., 2017).

As a treatment option for individuals with chronic heroin dependence who have not responded to traditional medication therapies, several countries have experimented with offering pharmaceutical-grade heroin as treatment for opioid use disorder. Today, heroin-assisted treatment (HAT) is available in 58 clinics across eight countries, with four countries offering HAT as part of the standard treatment system (Uchtenhagen, 2017). With the dramatic rise in overdose mortality related to heroin and synthetic opioids, there has been increased attention to the role of innovative harm reduction programs for combatting the rising social costs of the opioid crisis (Ciccarone, 2017). This has included calls for action by both researchers and policymakers to expand access to conventional medication treatments for opioid use disorder as well as alternative therapies such as injectable heroin or hydromorphone (Fairbairn et al., 2017; 2017; Lavitt, 2015). While evidence from European countries and Canada have supported the potential benefits of HAT, the treatment remains controversial, with a range of concerns regarding therapeutic, social, and economic aspects (Uchtenhagen, 2017).

The purpose of this study is to provide a comprehensive overview of existing scientific evidence for HAT through a systematic review of the literature. We adopt a structured approach to review a range of outcomes, broadly classified as patient-level, community-level, and economic. We begin with an overview of systematic reviews regarding HAT efficacy for patient-level outcomes. This overview is complemented by discussion of evidence from source randomized controlled trials (RCT) studies contributing to the included reviews and supplementary evidence from additional studies captured through our literature search. While we prioritize RCT evidence for our review of HAT's comparative effectiveness for patient-level outcomes, we adopt broader inclusion criteria to provide narrative reviews synthesizing existing evidence on community-level and economics outcomes associated with HAT.

The paper is organized as follows. Chapter 2 describes the methods used for the literature search, and Chapter 3 presents the search results and describes the included systematic reviews and RCTs. Chapter 4 presents an overview of systematic reviews on the effects of HAT for patient-level outcomes, complemented by a narrative review of source studies and supplementary evidence. Chapter 5 and 6 review the evidence for how HAT affects community-level and cost outcomes, respectively. Finally, Chapter 7 summarizes findings.

2. Methods

Search Strategy

Five electronic databases were searched from 1990 until January 17, 2018: PubMed, Embase, Web of Science, Scopus, and WorldCat for books, reports, and other "grey literature."[3] The databases were searched using combinations of the following terms: "heroin assisted," "pharmaceutical heroin," "diacetylmorphine," "diamorphine," "maintenance," "therapy," "treatment," "dependence," or "disorder" (see **Appendix B** for exact search strategy). No language restrictions were imposed. We also screened reference lists of systematic reviews and narrative reviews identified during the study selection process and conducted forward and backward searches on key articles. Finally, experts in the field who were participating in interviews for the project were given the opportunity to pass along any articles they believed to be of particular relevance.

Inclusion and Exclusion Criteria

Our broad search strategy was intended to capture a wide range of literature to support this review's evaluation of the evidence base for the effects of heroin-assisted treatment on patient-level, community-level, and economic outcomes.

To assess the evidence base for how heroin-assisted treatment impacts individual- or patient-level outcomes, we first performed an overview of systematic reviews. We defined systematic reviews as those that had explicit criteria for study inclusion or exclusion, and used a systematic process for screening studies for inclusion and extracting data from included studies. Reviews were eligible if they included heroin-assisted treatment for opioid dependence as one of the included interventions (i.e., systematic reviews reporting solely on other non-heroin pharmacological treatments for opioid use disorder, such as methadone or slow release oral morphine, were not included) and reported on patient-level outcomes. No restrictions were placed on comparators, setting, or participant characteristics. Given heterogeneity in RCT implementation and the potential for overlap across systematic reviews, we also confirmed whether individual source studies were picked up from our original search and extracted data from them. In addition, we reviewed the results from our literature search to check for evaluations of patient-level outcomes from RCTs published after the search period of the most recent systematic review. For reviewing evidence for longer-term outcomes, we adopted more

[3] *Grey literature* refers to sources not published by a commercial publisher, such as government reports and civil society publications. For a more detailed definition, see Grey Literature Report, New York Academy of Medicine, undated.

flexible inclusion criteria to additionally include evidence from non-RCTs, although we discuss these separately.

To assess the evidence base for community-level and cost outcomes, we reviewed our search results for both systematic reviews and individual studies assessing the economic or community-level impact. While we prioritized evidence from systematic reviews or RCTs, we allowed broader inclusion criteria for these outcomes. Specifically, since the community is not the unit of randomization in any RCT, we also considered quasi-experimental studies examining the impact of heroin-assisted treatment provision on community-level or neighborhood outcomes. To capture studies discussing the costs of heroin-assisted treatment provision, we included studies evaluating economic outcomes that 1) used an RCT design, 2) used a modelling approach with at least some parameter estimates derived from RCT findings, or 3) described empirical evidence on the costs of HAT provision; with the latter of these discussed separately from the RCT findings.

Study Selection Process

Search results were first screened by title and abstract. Based on titles and abstracts, citations were flagged as either a potential systematic review or an individual study of outcomes. Any citation considered potentially relevant was retrieved in full text and reviewed to determine whether it met the selection criteria. Questions about the relevance of any study were resolved through discussion with other research team members.

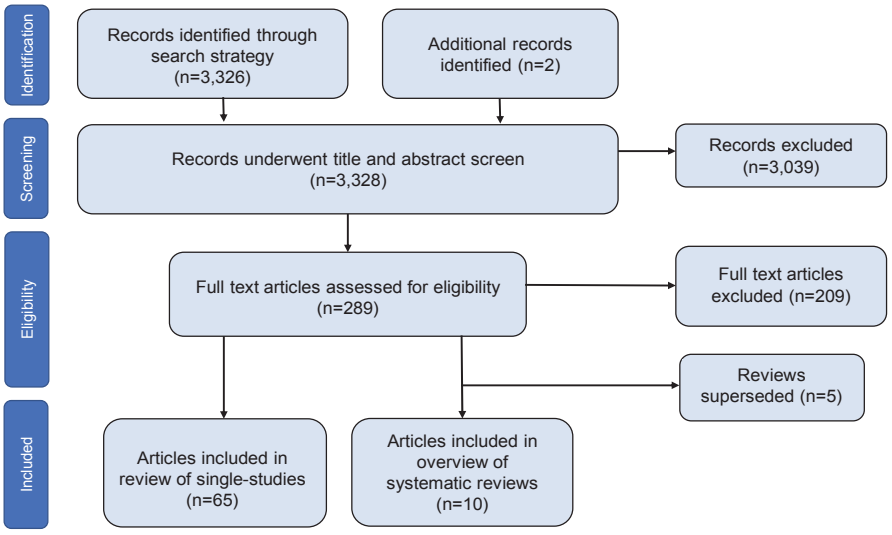
Data Extraction

The reviewer extracted data from each study using an electronic template that was developed for this study prior to the literature search. Separate templates were used for reviews and for individual studies. Extracted data for reviews included general article information (e.g., authors, year of publication, source of article); research question and/or objective of the review; details on review content (e.g., setting, years and databases searched, study eligibility criteria, number of studies, and number of participants); and information on outcome measures, whether a meta-analysis was conducted, and study conclusions. Extracted data for single studies included similar information except details on study content were focused on study period, study design and analytic approach, definition of intervention and control groups (where applicable), and participant eligibility.

3. Search Results for Heroin-Assisted Treatment (HAT)

Figure 1 depicts the process by which studies were reviewed for eligibility. Our search strategy for heroin-assisted treatment yielded 3,326 de-duplicated records. We also became aware of two relevant studies (Bansback et al., 2018; Nikoo et al., 2018) evaluating the results of heroin-assisted treatment RCTs published after the end period of our database search, resulting in a total of 3,328 records. Based on the title and abstract screening, we excluded 3,039 of these documents as not meeting our inclusion criteria. Primary reasons were that the document evaluated other kinds of treatment (e.g., buprenorphine or methadone); discussed the history or context of heroin-assisted treatment with limited analysis of outcomes at the individual, community, or societal level; or was not an empirical study or literature review (e.g., commentaries or editorials).

Figure 1. Flow diagram of studies included in review of heroin-assisted treatment literature



Of the 289 documents retained for full-text review, 15 met our eligibility criteria as a systematic review of patient-level treatment outcomes (three others were systematic reviews of economic outcomes). Five of the 15 reviews were excluded because they were superseded by a more recent systematic review by the same authors. A list of the superseded reviews as well as

reviews excluded following the full text screen and description of reasons for exclusion are provided in **Appendix B**.

Sixty-five additional documents retained for full-text review met our inclusion criteria for individual studies. **Table 2** outlines how many of these included records were source studies (i.e., studies captured in identified systematic reviews) or additional articles that met our inclusion criteria but were not noted in any of the included systematic reviews. The primary reasons for excluding individual studies were: studied an alternative pharmacological treatment for opioid use disorder, focused on stakeholder perspectives regarding heroin-assisted treatment, or were commentaries or contextual overview pieces without empirical analyses. The majority of included individual studies evaluated patient-level outcomes (n=55), with a much more limited evidence base for economic (n=7) and community-level outcomes (n=5). While most included studies used an RCT design, because there have only been 10 main HAT RCTs, multiple articles are drawing from the same evidence base. For instance, results from the same RCT often spanned numerous articles because the research team published results for different outcomes or different subgroups as separate products, or separately published mediation analyses.

Table 2. Included Articles, by Outcome Domain

	Patient-level	Community-level	Economic
Number of included systematic reviews	10	0	3
Number of included individual articles [a]	55	5	7
Number of included source articles	25	N/A	4
Number of included supplementary articles	30	5	3

Notes: [a]One article spans all three outcome domains.

Description of Included Systematic Reviews

One of the ten reviews that met inclusion criteria for patient-level treatment outcomes was an overview of systematic reviews (Amato et al., 2005). Table 3 briefly describes the other nine (Ali et al., 2017; Dalsbo et al., 2010; Egli et al., 2009; Ferri et al., 2011; Fingleton et al., 2015; Koehler et al., 2014; Perry et al., 2015; Strang et al., 2015; Timko et al., 2016).

Publication date and format. All nine reviews were published between 2009 and 2017, and over half (n=5) were published from 2015 onward. Five were published as peer-reviewed journal articles, two as Cochrane reviews (Ferri et al., 2011; Perry et al., 2015), one as a Campbell review (Egli et al., 2009), and one as a research report (Dalsbo et al., 2010). The number of heroin-assisted treatment studies included in each review ranged from one (Perry et al., 2015) to eight (Ferri et al., 2011).

Study design inclusion. Six of the nine only included results from RCTs (Ali et al., 2017; Dalsbo et al., 2010; Ferri et al., 2011; Perry et al., 2015; Strang et al., 2015) or from controlled evaluations (Koehler et al., 2014). One only included RCTs and national cohort studies that had a follow-up period of at least 12 months (Fingleton et al., 2015). Another included all comparative studies, but evidence from RCTs was analyzed separately from evidence derived from non-RCT designs (Timko et al., 2016). Finally, Egli et al. (2009) included pre-post studies, comparison studies with a randomized or quasi-experimental design, as well as macro-level studies evaluating the impact on community-level outcomes; RCTs were analyzed separately from studies with other designs.

Interventions. Three reviews focused on evaluating evidence for heroin-assisted treatment specifically (Dalsbo et al., 2010; Ferri et al., 2011; Strang et al., 2015). Five evaluated a wider range of pharmacological treatments for the treatment of opioid use disorder (Ali et al., 2017; Egli et al., 2009; Fingleton et al., 2015; Perry et al., 2015; Timko et al., 2016). Koehler et al. (2014) employed even broader criteria, considering interventions that targeted drug use and related behaviors among those who misuse illicit drugs; while interventions were not required to have a treatment focus or to target opioid use disorder, the majority of included interventions involved opioid agonist therapies for the treatment of opiate dependence.

Comparators. One review explicitly imposed restrictions on the control interventions, requiring standard methadone treatment as the comparator (Ali et al., 2017). All other reviews allowed a variety of comparators (e.g., no intervention, methadone, waiting list, other pharmacological and/or psychosocial treatments).

Participants and Setting. While few reviews explicitly specified participant inclusion criteria, because of the nature of the interventions of interest, included participants in most studies were effectively restricted to adults with opioid use disorder. Two reviews limited participants to criminal offenders who misuse illicit drugs (Koehler et al., 2014; Perry et al., 2015). Only one review restricted its eligibility criteria based on setting, limiting the search to interventions conducted in Europe (Koehler et al., 2014). Of note, while the systematic review by Dalsbo et al. (2010) did not restrict study eligibility based on setting, the purpose of the review was to synthesize international evidence on heroin-assisted treatment in order to generate implications specific to the Norwegian context.

Outcomes. Collectively, the nine reviews addressed a broad range of patient-level outcomes, including retention in treatment, illicit or "street" use of heroin, use of other illicit drugs and/or alcohol, criminal activity or offenses, social or health functioning, medical adverse events, and mortality. Four reviews considered a broad set of patient-level outcomes (Ali et al., 2017; Dalsbo et al., 2010; Ferri et al., 2011; Strang et al., 2015) while five were more targeted, focusing on criminal activity or drug use (Egli et al., 2009; Koehler et al., 2014; Perry et al., 2015), mental health metrics (Fingleton et al., 2015), or treatment retention (Timko et al., 2016). The methods and tools used to assess outcomes varied substantially both across and within systematic reviews.

Meta-analyses. Four reviews incorporated meta-analyses (Egli et al., 2009; Ferri et al., 2011; Koehler et al., 2014; Strang et al., 2015). Two of these conducted random-effect meta-analyses to calculate pooled risk ratios for the outcomes of treatment retention, serious adverse events, and mortality (Ferri et al., 2011; Strang et al., 2015). The other two summarized effect sizes for criminal offending, presenting results based on both fixed-effects and random-effects models (Egli et al., 2009; Koehler et al., 2014). However, because the meta-analysis by Koehler et al. (2014) combines heroin-assisted treatment with a broad range of other treatments (e.g., naltrexone implants, drug testing, psychosocial care) in the computation of pooled effect sizes, we do not report results of their meta-analysis in our discussion.

Table 3. Summary Table of Scope of Included Systematic Reviews for Patient-Level Outcomes

Review (Year)	Years Search Covered	# (HAT) Studies Included	HAT study method eligibility
Egli et al. (2009)	1960 – 2009	46 (6)	RCTs, quasi-experimental studies, & pre-post studies
Dalsbo et al. (2010)	2005 – Mar 2010	8 (8)	High-quality systematic reviews & more recent RCTs
Ferri et al. (2011)	Until Nov 2009	8 (8)	RCTs
Koehler et al. (2014)	Not stated	14 (8)†	Controlled evaluations in Europe (any European language)
Fingleton et al. (2015)	1996 – 2011	22 (4)	RCTs & national cohort studies with follow-up of at least 12 months (English language)
Perry et al. (2015)	Until May 2014	14 (1)	RCTs
Strang et al. (2015)	Not stated	6 (6)	RCTs of supervised injectable heroin treatment (English language)
Timko et al. (2016)	2010 – 2014	55 (6)	Comparative studies (English language)
Ali et al. (2017)	2010 – Jun 2016	5 (2)	Intervention-based RCTs with methadone as comparator

Notes: HAT = Heroin assisted treatment. †Numbers listed here disagree with Table 1 of Koehler et al. (2014), which suggests 15 studies (10 HAT). We consider the Dutch trials as two instead of three separate studies, consistent with prior literature. Additionally, Koehler et al. (2014) appears to incorrectly list one study of dihydrocodeine (Robertson et al., 2006) as a study of HAT.

Description of the Heroin-Assisted Treatment RCTs

Our search results identified ten RCTs comparing HAT to other treatments for opioid use disorder (see **Table 4**). While the earliest of these RCTs, conducted in London in the 1970s, evaluated the effectiveness of unsupervised injectable HAT, the majority of RCTs have compared supervised HAT plus optional oral methadone to oral methadone alone. Two trials (one in the Netherlands and one recent RCT in Belgium) have considered supervised heroin prescription through different administration methods (injectable or inhalable), one arm of the UK Randomized Injectable Opioid Treatment Trial (RIOTT) study compared supervised injectable methadone to optimized oral methadone, and the recent Canadian Study to Assess Longer-term Opioid Medication Effectiveness (SALOME) trial compared the effectiveness of supervised injectable heroin to supervised injectable hydromorphone (following up on the pilot

findings of hydromorphone in the Canadian North American Opiate Medication Initiative [NAOMI] trial). In all, the trials have spanned seven countries (six European nations and Canada), nearly four decades of investigation, and have included just over 3,500 participants. Nearly 30% of participants come from just one large RCT in Germany (n=1015).

Table 4. Overview of Heroin-Assisted Treatment Randomized Controlled Trials

Trial (period)	Intervention condition (T)	Control condition (C)	Sample size	Duration (months)
Early UK trial (1972–1975)	Unsupervised injectable HAT + oral methadone	Oral methadone	T: 44 C: 52	12
Swiss trial (1995–1996)	Supervised injectable HAT + oral methadone	Other conventional drug treatment	T: 27 C: 24	6
Injectable Dutch trial* (1998-2001)	Supervised injectable HAT + oral methadone	Oral methadone	T: 76 C: 98	12
Inhalable Dutch trial* (1998–2001)	**T1**: Supervised inhalable HAT + oral methadone **T2**: Oral methadone for 6mo then inhalable heroin + optional oral methadone for 6mo	Oral methadone	T1: 117 T2: 119 C: 139	12
Spain PEPSA (2001–2004)	Supervised injectable HAT + oral methadone	Oral methadone	T: 31 C: 31	9
German study* (2002–2004)	Supervised injectable HAT + oral methadone and: **T1**: psychoeducation & counseling **T2**: case management & motivational interviewing	Oral methadone plus: **C1**: education & counseling **C2**: case management/MI	T1: 258 T2: 257 C1: 255 C2: 245	12
Canada NAOMI* (2005–2008)	**T1**: Supervised injectable HAT + oral methadone **T2**: Supervised injectable hydromorphone + oral methadone	Oral methadone	T1: 115 T2: 25 C: 111	12
UK RIOTT* (2005–2008)	**T1**: Supervised injectable HAT + oral methadone **T2**: Supervised injectable methadone + oral methadone	Optimized oral methadone	T1: 43 T2: 42 C: 42	6
Belgium TADAM (2011–2013)	Supervised injectable or inhalable HAT + oral methadone	Oral methadone	T: 36 C: 38	12
Canada SALOME (2011–2013)	Supervised injectable HAT + oral methadone	Supervised injectable hydromorphone + oral methadone	T: 102 C: 100	6

Notes: *Multi-site study. HAT=heroin-assisted treatment.

The purpose of these RCTs has not been to evaluate the potential for HAT to serve as a first-line treatment option or as a replacement for oral methadone. Instead, trials have largely focused on testing the effectiveness of HAT for a particular group of treatment-refractory individuals with a history of chronic heroin dependence and multiple prior attempts at conventional treatment modalities, primarily oral methadone. Most RCTs have thus had relatively stringent participant eligibility requirements that differ from those required to participate in conventional behavioral or medication treatments for opioid use disorder (see **Appendix Table A2** for details

on eligibility requirements). While there is some variation across the trials, participants have tended to be over age 35 and male; with a heroin use history that spans more than one decade; and at least three prior attempts at treatment for opiate dependence, primarily methadone. **Table 5** presents baseline characteristics for participants across the ten RCTs, all of which restricted study populations to adults.

The early UK trial included relatively broad eligibility criteria for opioid use or use disorder, requiring that individuals injected heroin daily for at least three months and exhibited a level of dependence severity sufficient to convince program staff that they qualified for HAT. Participant age at recruitment was restricted to 18-35, and there were no requirements for prior treatment history beyond persistently requesting HAT and rejecting alternative treatments. Therefore, participants from this trial tended to be younger and have shorter use careers relative to the other trials. Other drug use problems among participants in this early trial also tended to involve amphetamines and barbiturates; whereas participants in later trials tended to have polydrug use related to cocaine or benzodiazepines, reflective of changes in drug supply over time.

As shown in **Table 5**, participants in the more recent trials have had an average age over 30 – and in the most recent trials over 40. Males have made up over three-quarters of the participant population in all RCTS except the two Canadian trials. Following the early UK trial, the heroin use careers of RCT participants have also been lengthy, with average use careers ranging from 12 to 20 years. This may in part be due to eligibility requirements related to duration of opioid dependence and prior treatment history. The Swiss and Spanish RCTs required participants to have at least two years of opioid dependence and at least two prior treatment attempts. The Dutch, German, Belgian, and Canadian SALOME trials required at least five years of opioid dependence. Of note, while most trials place requirements on prior treatment episodes, both the Dutch trials and UK RIOTT required participants to have been regularly attending conventional oral methadone during the previous 6 months, but continuing to use heroin (semi-)regularly.

Participants have also exhibited relatively high-risk clinical profiles in terms of physical health, mental health, and criminal justice involvement. Several trials (Swiss, Dutch, Spanish, German, and Belgian) explicitly included poor health and social functioning as eligibility criteria. Participants' relatively long use careers also contribute to a sample population with relatively high rates of criminal justice involvement, injection-related infections (e.g., hepatitis B and C, HIV), and other problems related to health and social functioning.

Table 5. Baseline Characteristics of Participants in HAT Randomized Controlled Trials

Trial (# Participants)	Average Age	% Male	Average Duration Drug Use (Years)	Prior Treatment (Average or %)
Early UK RCT (n=96)	23.9	75%	Opiates: 5.9 Misuse of non-opiates: 8.2	Not stated
Swiss RCT (n=51)	31.9	75%	Injected heroin: 12	# drug treatment episodes: 8 # methadone treatment episodes: 3.2

Injectable Dutch trial (n=174)	38.5	82.2%	Heroin: 15.9 Cocaine: 16.6	Years regular methadone use: 12.1
Inhalable Dutch trial (n=375)	39.6	79.7%	Heroin: 16.7 Cocaine: 14.6	Years regular methadone use: 12.4
Spanish PEPSA (n=62)	37.2	90.3%	Heroin: 19	# methadone treatment episodes: 3.1
German RCT (n=1015)	36.4	79.9%	Heroin: 13.6 Cocaine: 5.5 Benzodiazepines: 5.2	Any medication treatment: 89.3%
Canadian NAOMI (n=251)	39.7	61.4%	Injected drugs: 16.5	# drug treatment episodes: 11.1 # methadone treatment episodes: 3.2
UK RIOTT (n=127)	37.2	73.4%	Opiates: 16.5 Injected drugs: 13.7	# treatment episodes: 4.4
Belgian TADAM (n=74)	43.0	87.8%	Heroin: 20	# treatment episodes: 9
Canadian SALOME (n=202)	44.3	69.3%	Injected heroin: 15.4	# methadone treatment episodes 5.1

Notes and sources: Descriptive statistics were reproduced or calculated based on a combination of articles included in our literature review

The RCTs have also varied with respect to medication dosages provided across treatment arms. **Table 6** presents descriptive statistics on dosage levels across the trials. Among the control conditions, oral methadone doses have varied widely, ranging from an average of about 60 mg/day in the earlier trials to over 100 mg/day in the UK RIOTT's optimized oral methadone control condition. Examining the HAT groups, the lowest dosage (30-120 mg per day) was observed in the early UK trial for unsupervised injectable heroin. For studies of supervised HAT, the Spanish PEPSA trial exhibited the lowest average dose (<300 mg/day) and the Belgian TADAM trial the highest average dose (573 mg/day). However, HAT doses tend to taper over the study period; for instance, by the end of the 12-month trial period, HAT participants in the Belgian trial were receiving an average of 355 mg/day.

Table 6. Details of Treatment Conditions in Heroin-Assisted Treatment Randomized Controlled Trials

Trial	HAT intervention dosage		Control dosage
	Heroin dose/day	**Oral methadone dose/day**	**Oral methadone dose/day**
Early UK	Average: 60 mg Range: 30-120 mg	Unspecified	Average: 60 mg Range: 10-120 mg
Swiss trial	Average: 509 mg Quartiles: (400, 480, 630 mg)	Unspecified	Unspecified
Dutch injectable & inhalable trials	Average: 444.1 mg 95% CI: 357.4-530.7 mg Visits/day: average 1.7 in last month of treatment	Average: 58.3 mg 95% CI: 46.5-70.1 mg Max imposed: 150 mg	Average: 59.9 mg 95% CI: 55.2-64.5 mg Max imposed: 150 mg

	Max imposed: 1000 mg		
Spain PEPSA	Average: 274.5 mg Range: 15-600mg	Average: 42.6 mg Range: 18-124 mg	Average: 105 mg Range: 40-180mg
German study	Average: 442 mg	Average (days received): 39 mg Average (all days): 8 mg	Average: 99 mg Min imposed: 60 mg
Canada NAOMI	Average (no methadone): 392.3 mg Average (w/ methadone): 365.5 mg Max imposed: 1000 mg	Average: 34.0 mg	Average: 96.0 mg
UK RIOTT	Average: 398.9 mg SD: 163.6 mg Max imposed: 900 mg	Average: 41.8 mg SD: 12.7 mg	Average: 107.3 mg SD: 39.9 mg Doses >100 mg generally encouraged
TADAM	Average: 573 mg Visits per day: 2.3	Average: 20 mg	Average: 77 mg
SALOME	Average total-dose: 506.4 mg Range: 51-933.2 mg Max imposed: 1000 mg Visits per day: 2.5	Average (days received): 23.6 mg	**Injectable hydromorphone:** Average total-dose: 261.18 mg Range: 82.65-497.85 mg Visits per day: 2.3

Notes: Statistics compiled from a variety of articles included in the systematic review.

Given the shorter half-life of heroin, participants receiving supervised heroin could generally visit clinics up to three times daily to receive an injection. In all trials, the HAT participants were also given the opportunity to take home oral methadone in order to stave off withdrawal symptoms. In control groups receiving oral methadone, participants generally had to visit the clinics once in the morning to receive methadone. Participants in the RCTs have been offered a range of medical and psychosocial services in addition to study medications. Thus, while the objectives of HAT provision have been similar across all RCTs, the results of this review should be considered in light of heterogeneity in the context, design, and implementation of the trials (Fischer et al., 2007).

4. Results for Evidence of Effectiveness for Patient-Level Outcomes

Findings from the One Previous Overview of Systematic Reviews

We identified one prior overview of systematic reviews (Amato et al., 2005) that summarized the findings of five Cochrane reviews of the effectiveness of medication treatments for opioid use disorder with respect to patient-level outcomes; one of these focused on comparing HAT with other treatments (Ferri et al., 2003). Overall, when comparing HAT with other conventional drug treatments (primarily oral methadone), Amato et al. (2005) found no significant differences in treatment retention and little evidence to suggest a differential effect on illicit use of heroin, mortality, quality of life, or criminal activity. However, based on Ferri et al.'s (2003) systematic review that included 3 studies, 4 trials, and 577 participants, Amato et al. (2005) concluded there were differences based on the type of HAT. In particular, for patients who had previously not responded to oral methadone or who had persistently rejected conventional drug treatments, methadone treatment was significantly more effective for retaining patients than HAT when heroin was offered together with methadone, both for injectable heroin (RR = 1.17, 95% CI = 0.99–1.38) and for inhalable heroin (RR = 1.27, 95% CI = 1.11–1.46). But methadone was found to be significantly less effective than injectable HAT when heroin was offered alone (RR = 0.35, 95% CI = 0.21–0.59).

This seemingly contradictory result may derive from drawing conclusions from one systematic review of only a few HAT trials, which varied in the specific interventions and control conditions assessed. Furthermore, the three studies informing the conclusions of Amato et al. (2005) all had varying participant eligibility requirements regarding prior treatment experience: one necessitated persistent rejection of non-HAT treatment modalities (Hartnoll et al., 1980), one required participants to have undergone "two or more previous unsuccessful attempts at drug treatment" (Perneger et al., 1998), and one required participants to be regularly attending methadone treatment but continuing to use heroin on a (near-)daily basis (van den Brink et al., 2003). However, Ferri et al.'s (2003) study has since been updated, and several newer systematic reviews have been published. We next describe findings based on the nine systematic reviews we identified, all of which are more recent than Amato et al. (2005).

Findings from the Nine Systematic Reviews

As shown in Table 7, the nine systematic reviews draw on a relatively small number of original studies. While the nine reviews considered evidence from 25 different articles, those 25 articles were based on just nine RCTs of HAT and four non-RCT studies. There was

considerable overlap in which studies the reviews included, with eight of the nine RCTs being considered by multiple reviews.

The most commonly studied patient-level outcomes were criminal activity or criminal offenses (Ali et al., 2017; Egli et al., 2009; Ferri et al., 2011; Koehler et al., 2014; Perry et al., 2015) and illicit drug use (Ali et al., 2017; Dalsbo et al., 2010; Ferri et al., 2011; Koehler et al., 2014; Strang et al., 2015), followed by treatment retention (Dalsbo et al., 2010; Ferri et al., 2011; Strang et al., 2015; Timko et al., 2016) and social or health functioning (Ali et al., 2017; Dalsbo et al., 2010; Ferri et al., 2011; Fingleton et al., 2015). Three reviews evaluated evidence for effects on serious medical adverse events and mortality (Dalsbo et al., 2010; Ferri et al., 2011; Strang et al., 2015).

Table 7. Overlap of Heroin-Assisted Treatment Studies Included in Systematic Reviews of Patient-Level Outcomes, by Outcome

	Illicit Drug Use					Treatment Retention				Criminal Activity					Social or Health Function				Adverse Events			Death		
	Dalsbo et al. (2010)	Ferri et al. (2011)	Koehler et al. (2014)	Strang et al. (2015)	Ali et al. (2017)	Dalsbo et al. (2010)	Ferri et al. (2011)	Strang et al. (2015)	Timko et al. (2016)	Egli et al. (2009)	Ferri et al. (2011)	Koehler et al. (2014)	Perry et al. (2015)	Ali et al. (2017)	Dalsbo et al. (2010)	Ferri et al. (2011)	Fingleton et al. (2015)	Ali et al. (2017)	Dalsbo et al. (2010)	Ferri et al. (2011)	Strang et al. (2015)	Dalsbo et al. (2010)	Ferri et al. (2011)	Strang et al. (2015)
RCT Studies																								
UK (1970s): Unsupervised injectable HAT	X	X	X			X	X			X	X	X			X	X						X	X	
Swiss (95-96): Supervised injectable HAT	X	X	X	X		X	X	X		X	X	X			X	X	X					X	X	X
Netherlands (98-01):* Supervised injectable HAT		X	X	X		X				X	X	X									X	X	X	X
Netherlands (98-01):* Supervised inhalable HAT		X	X			X				X	X	X										X	X	
Spain (2003-04): Supervised injectable HAT	X	X	X	X		X	X			X	X	X			X	X	X		X	X	X	X	X	X
Germany (2002-04) * Supervised injectable HAT	X	X	X	X		X	X	X	X	X	X	X	X			X	X		X		X	X	X	X
Canada (2005-08):* Supervised injectable HAT	X	X		X		X	X	X	X		X				X	X	X		X	X	X	X	X	X
UK RIOTT (2005-08):* Supervised injectable HAT	X	X		X	X	X	X	X	X										X	X	X	X	X	X
Belgium (2011-13): Supervised injectable HAT					X									X				X						
Non-RCT Studies																								
UK: McCusker and Davies (1996)			X									X												
UK: Metrebian (2001)			X									X												
Swiss: Killias et al. (1999)										X														
Netherlands: Blanken et al. (2010a)									X															

# Studies		6	8	8	6	2	8	6	4	4	6	7	8	1	1	2	5	4	1	4	3	5	8	8	6
# RCTs		6	8	6	6	2	8	6	4	3	5	7	6	1	1	2	5	4	1	4	3	5	8	8	6

Notes: *Multicenter or multi-site randomized controlled trials (RCTs).

As the majority of source studies informed the conclusions of more than one review, the following presentation describes both the findings of the reviews as well as the individual source studies based primarily on information reported in the reviews but supplemented with extracted information from the source studies captured in our literature search.

Treatment Retention

Four of the nine systematic reviews evaluated the effectiveness of heroin-assisted treatment on retention in treatment (Dalsbo et al., 2010; Ferri et al., 2011; Strang et al., 2015; Timko et al., 2016), where retention was defined as having remained in treatment by the end of the trial period. These four reviews spanned eight RCTs and one prospective cohort study. Study arm length among the included RCTs ranged from 6 to 12 months, while the prospective cohort study assessed four-year treatment retention among HAT patients with no comparator.

Based on evidence from eight trials (n=2032 participants) comparing heroin treatment (in all but one case, injectable heroin treatment) to traditional medication treatment, Dalsbo et al. (2010) concluded that the evidence was uncertain. While the reviewed studies generally supported higher rates of treatment retention among HAT patients, the authors deemed the included studies to be of low quality due to unclear items in risk of bias, potential for publication bias, and imprecision of effect sizes.

Ferri et al. (2011) evaluated treatment retention based on the same trials as Dalsbo et al. (2010), with the exception that Ferri et al. (2011) dropped the two Dutch trials due to potential bias. Those two Dutch trials subjected HAT patients to stricter disciplinary discharge rules that led to six percent of the HAT group being discharged from treatment (van den Brink et al., 2003). Based on the remaining six studies, Ferri et al. (2011) concluded that the evidence supports heroin as more effective for treatment retention among patients who have not responded to conventional treatments, with meta-analytic results (RR = 1.44; 95% CI = 1.16, 1.79) driven primarily by trials comparing supervised injectable heroin with oral methadone. However, their pooled analyses exhibit significant heterogeneity between trials.

Strang et al. (2015) reached similar conclusions in favor of supervised injectable heroin for treatment retention (RR=1.37; 95% CI = 1.03, 1.83) based largely on the same group of studies. However, unlike Ferri et al. (2011), Strang et al. (2015) excluded the statistically insignificant effect shown in the Spanish PEPSA trial because the oral methadone group was automatically offered the option of starting supervised injectable heroin at the end of the trial.

Focusing on a smaller set of more recent studies published after 2010, Timko et al. (2016) similarly concluded that, compared to oral methadone, heroin-assisted treatment was associated with higher treatment retention rates among treatment-refractory patients with opioid dependence. While the review included a few studies comparing supervised injectable heroin to treatments other than oral methadone, findings from these studies were not explicitly discussed in the review's conclusions.

Table 8 reports the results of the original source studies that were included in the three reviews just discussed, specifically the risk ratios and 95% confidence intervals. For a few overlapping source studies (Hartnoll et al., 1980; Oviedo-Joekes et al., 2009a; Perneger et al., 1998), reviews computed slightly different estimated risk ratios. For completeness, all are reported in the Table.

Table 8. Comparison of Heroin-Assisted Treatment versus Control Treatments from Source Studies, Retention in Treatment

Experimental v Control Condition	Included in Review:				Experimental	Control	
Study: Treatment Duration	**Dalsbo**	**Ferri**	**Strang**	**Timko***	**Events/Total**	**Events/Total**	**RR [95% CI]**
Unsupervised injectable heroin v oral methadone							
Early UK trial: 12 months		X			32 / 44	15 / 52	2.52 [1.59, 4.01]
Early UK trial: 12 months	X				31 / 44	13 / 52	2.82 [1.70, 4.68]
Supervised injectable heroin (+ oral methadone) v other drug treatment							
Swiss trial: 6 months		X			27 / 27	22 /24	1.09 [0.95, 1.26]
Swiss trial: 6 months	X		X		25 / 27	22 / 24	1.01 [0.86, 1.19]
Supervised injectable heroin (+ oral methadone) v oral methadone							
German trial: 12 months	X	X	X		346 / 515	200 / 500	1.68 [1.48, 1.90]
NAOMI: 12 months		X			77 / 115	45 / 111	1.65 [1.27, 2.14]
NAOMI: 12 months	X		X		101 / 115	60 / 111	1.62 [1.35, 1.95]
UK RIOTT: 6 months	X	X	X	X	38 / 43	29 / 42	1.28 [1.02, 1.61]
Spain PEPSA: 9 months	X	X			23 / 31	21 / 31	1.10 [0.80, 1.51]
Dutch injectable trial: 12 months	*X*				*55 / 76*	*83 / 98*	*0.85 [0.73, 1.01]*
Supervised inhalable heroin (+ oral methadone) v oral methadone							
Dutch inhalable trial: 12 months	*X*				*80 / 117*	*121 / 139*	*0.79 [0.68, 0.90]*
Supervised injectable heroin (+ oral methadone) v supervised injectable hydromorphone (+ oral methadone)							
NAOMI: 12 months				X	101 / 115	22 / 25	1.00 [0.85, 1.17]
Supervised injectable heroin (+ oral methadone) v supervised injectable methadone (+ oral methadone)							
UK RIOTT: 6 months				X	38 / 43	29 / 42	1.09 [0.91, 1.31]

Notes: *As Timko et al. (2016) presented rates but not risk ratios, information on counts was drawn from our review of the source studies, from which we calculated risk ratios and 95% confidence intervals.

Three of the source studies comparing supervised injectable heroin to oral methadone found that HAT was significantly more effective for retaining patients in treatment. In the large German trial (Haasen et al., 2007), 67% of the HAT group completed 12 months of treatment whereas only 40% of the methadone group did. The average number of treatment days was also higher, at 290 days compared to 195 days. In the Canadian NAOMI trial (Oviedo-Joekes et al., 2009a), treatment retention rates at 12-month follow-up in the heroin group were 88%, significantly higher than the 54% rate in the methadone group. Finally, the UK RIOTT trial (Strang et al., 2010), which had a shorter treatment duration of 6 months, similarly showed higher treatment retention for injectable heroin relative to oral methadone, although differences between the groups (81% vs. 69%) were smaller than in the trials with longer treatment duration. The two trials finding insignificant treatment retention differences between supervised injectable heroin and other treatments (primarily oral methadone) were smaller studies and had treatment durations less than 12 months.

While the two Dutch trials suggested that HAT (injectable and inhalable) was less effective than oral methadone for retaining patients in treatment at 12 months, the differential application of discharge rules across the experimental and control conditions may have biased these results. While we did not identify any studies detailing the disciplinary rules across treatment arms, van den Brink and Blanken (2002) noted that serious or repeated violation of the following "house rules" may have resulted in exclusion from the heroin treatment program: no use of drugs other than study medications in the treatment center, no use of any drugs in the vicinity of the treatment center, and no attempts to remove prescribed heroin from the administration rooms or treatment center. It is plausible that similar rules may be applied to a wider implementation of HAT, particularly in jurisdictions facing concerns about the potential community impact of establishing HAT centers. Furthermore, the NAOMI trial also had evidence of disproportionate exclusion due to violations of clinic rules in the HAT arm (15% in HAT vs <1% in oral methadone); as did the Belgian TADAM trial (14% in HAT vs. 0% in methadone).

Two studies comparing supervised injectable heroin to other injectable opioids found insignificant differences for treatment retention. The NAOMI trial had a small double-blind pilot arm comparing supervised injectable heroin to supervised injectable hydromorphone (Oviedo-Joekes et al., 2010b). Retention rates at 12-months were 88% for both groups. Similarly, in a comparison of supervised injectable heroin to supervised injectable methadone within the UK RIOTT study, treatment retention rates at 6 months did not differ, although the authors note that the study was not powered to compare these two treatment conditions (Strang et al., 2010).

When considering the results for treatment retention, it is critical to bear in mind that the comparative effectiveness of HAT relative to oral methadone is being assessed for a population of patients who have (for the most part) previous attempts with the control condition treatment or who have persistently rejected existing available treatments. Indeed, in several trials showing the greatest relative benefit of HAT, substantial dropout from the control group occurred proximately to being assigned to the control condition, not midway through treatment. As shown

in Table 8, the early UK RCT found the largest divergence in treatment retention across groups (Hartnoll et al., 1980), with 74% of the HAT group retained at 12 months vs. 30% for the group receiving oral methadone only. However, 12% of the oral methadone group left treatment immediately following their randomization. It was also the only study of *unsupervised* heroin distribution. Similarly, the German trial reported that 28.8% of those assigned to oral methadone dropped out before even beginning treatment (compared to 2.3% of those assigned to HAT) (Haasen et al., 2007). Likewise, the UK RIOTT study reported patients assigned to the oral methadone condition were significantly less likely to begin treatment than those assigned to injectable heroin (Strang et al., 2010). In the recent Belgian TADAM trial, 18 of 38 individuals (47%) allocated to the control oral methadone condition failed to show up to their allocated treatment center (Demaret et al., 2015).

One debate about how to interpret evidence on treatment retention stems from some studies counting individuals as retained even if they switch treatment methods. Since individuals assigned to HAT can switch to the methadone treatment arm but the converse was not permitted, some have argued that estimates of treatment effectiveness are biased in favor of the heroin treatment arm (Kahan et al., 2011). For instance, in the NAOMI trial, 20% (n=23) individuals assigned to the heroin-assisted treatment group transferred to oral methadone before the end of the 12-month study period (Oviedo-Joekes et al., 2009a). If those 23 individuals were not coded as having been retained, then the risk ratios would be much closer to 1.

However, others have countered that switching from HAT to methadone should be considered a positive treatment outcome (Schechter and Kendall, 2011). Indeed, in the NAOMI trial, heroin-assisted patients were encouraged to transfer to methadone and in other trials, the rates of switching have been substantially lower. One person (3.7%) randomized to HAT in the Swiss trial requested transfer to oral methadone one day after receiving heroin treatment (Perneger et al., 1998), and two individuals (6.5%) randomized to HAT in the Spanish PEPSA trial voluntarily dropped out to undertake regular oral methadone treatment (March et al., 2006). In the recent Belgian TADAM trial, two (6%) of participants assigned to HAT referred themselves to methadone or abstinence-based treatment before the end of the 12-month trial period. Understanding the optimal duration of HAT before patients can effectively transition to other treatment modalities may help clarify how to appropriately embed HAT within a broader system of treatment.

Illicit drug use

Five of the nine systematic reviews evaluated the comparative effectiveness of HAT for reducing illicit drug use (Ali et al., 2017; Dalsbo et al., 2010; Ferri et al., 2011; Koehler et al., 2014; Strang et al., 2015). However, because Koehler et al. (2014) grouped HAT with a variety of other treatment modalities for the outcome of illicit drug use, we exclude that review. The four remaining reviews spanned nine RCTs. Two (Ali et al., 2017; Strang et al., 2015) examined illicit or “street” heroin use as a specific outcome, and two evaluated illicit drug use more

broadly with discussion of changes in illicit heroin use where applicable (Dalsbo et al., 2010; Ferri et al., 2011).

All four found HAT was more effective than oral methadone for reducing illicit heroin use, although the reviews interpreted these findings with varying degrees of certainty. The two reviews that specifically assessed illicit use of non-opiate drugs concluded findings were mixed. As noted by all reviews, the individual source studies ranged widely in how illicit drug use was measured, and thus no meta-analyses were reported. The measures and general findings of the source studies included in the reviews are presented in **Table 9**. Drug use was assessed differently across RCTs, with the majority relying on combined evidence from participant self-report and urinalysis (see **Appendix A**). Given heterogeneity in outcome measurement, we discuss findings from each of the source studies separately.

Table 9. Comparison of Heroin-Assisted Treatment to Control Treatment Condition among Source Studies Included in Systematic Reviews, Findings for Illicit Drug Use

Experimental v Control		Experimental		Control		Findings
Study: Follow-up	**Illicit drug use measure**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	
Unsupervised injectable heroin v oral methadone						
Early UK trial: 12 months	(Near) daily use illicit opiates in past month:	NR	27 / 42	NR	27 / 46	p > 0.05
	Non-opiate substance use (primarily barbiturates and amphetamines)	NR	NR	NR	NR	p > 0.05
Supervised injectable heroin (+ oral methadone) v other drug treatment						
Swiss trial: 6 months	Daily use in past month: Street heroin	27 / 27	1 / 27	19 / 21	10 / 21	p = 0.002
	Other opiates	2 / 27	0 / 27	1 / 21	0 / 21	p = 1.00
	Alcohol	6 / 27	5 / 27	3 / 21	4 / 21	p = 1.00
	Tobacco	25 / 27	26 / 27	21 / 21	20 / 21	p = 1.00
	Cannabis	6 / 27	4 / 27	1 / 21	3 / 21	p = 0.49
	Cocaine	1 / 27	1 / 27	2 / 21	2 / 21	p = 1.00
	Barbiturates	4 / 27	2 / 27	3 / 21	3 / 21	p = 1.00
	Benzodiazepines	12 / 27	0 / 27	9 / 21	7 / 21	p = 0.049
Supervised injectable heroin (+ oral methadone) v oral methadone						
Dutch trial: 12 months	Average days illicit heroin use during past month¥	Mean difference (HAT–methadone): –13.0 days; 95% CI: [–16.3, –9.6]				p < 0.05
Spain PEPSA: 9 months	Days street heroin use in past month: Mean (standard deviation)	24.5 (8.6)	8.3 (10.5)	23.3 (10.5)	16.9 (12.0)	p = 0.020
German trial: 12 months	>50% negative specimens for street heroin and no increase in cocaine use in the past month	NR	356 / 515	NR	276 / 500	p < 0.001

NAOMI: 12 months	Use street heroin at least one day of past month	NR	54 / 115	NR	79 / 111	p < 0.05
	Average days illicit heroin use in past month	26.6	5.3	27.4	12.0	p < 0.001
	Average days cocaine use in past month[†]	17.5	17.5	15	14	p > 0.05
UK RIOTT: 6 months	>50% negative specimens for street heroin over past 12 weeks	NR	28 / 43	NR	8 / 42	p < 0.001
	Zero positive specimens for street heroin over past 12 weeks	NR	5 / 43	NR	1 / 42	p = 0.100
	Self-reported abstinence from street heroin in past month	NR	22 / 43	NR	7 / 42	p = 0.001
Supervised injectable heroin or methadone (+ oral methadone) v oral methadone						
UK RIOTT: 6 months	>=50% negative specimens for street heroin over past 12 weeks	NR	28 / 43	NR	14 / 42	p = 0.003
Supervised injectable or inhalable heroin (+ oral methadone) v oral methadone						
Belgium TADAM: 12 months	Average days illicit heroin use in past month	27 days	8 days	28 days	16 days	p < 0.001
	With use of cocaine in past month	14 / 36	NR	20 / 38	NR	p > 0.05
	With use of benzodiazepine in past month	18 / 36	NR	13 / 38	NR	p = 0.022
Supervised inhalable heroin (+ oral methadone) v oral methadone						
Dutch trial: 12 months	Average days illicit heroin use during past month[¥]	Mean difference (HAT–methadone): –13.9 days; 95% CI: [–16.6, –11.2]				p < 0.05

Notes: NR=Not reported. [¥]Estimates were not directly reported in the source study but were provided in Ferri et al. (2011). [†]Estimates were not directly reported in the source study but were shown in figures; hence, the estimates in this row are approximate based on visual inspection of the figures.

As outlined in **Table 9,** only one study comparing HAT to oral methadone found no significant difference between the two groups for changes in illicit opiate use. Namely, the early UK trial allowing unsupervised injectable heroin showed no significant difference for the outcome of daily average of illicit opioid use during the past 12 months, measured by interviews and regular urine samples taken over the trial. Of note, a relatively high proportion of both groups were continuing to use illicit opiates regularly (59–64%), and 12% (n=5) of those in the HAT group reported selling part of their prescription. If total opiate consumption was considered (i.e., by summing amount of prescribed opiates and amount of illicit opiate use), the oral methadone group was significantly more likely to have stopped regular opiate use (<5 mg/day on average; two or fewer times per week) at 12-month follow-up.

In contrast, the later trials comparing supervised injectable heroin to oral methadone all found significantly greater reductions for illicit opiate use among those receiving supervised injectable heroin. Based on self-report data, the Swiss trial found reductions in past-month use of street heroin across both groups (Perneger et al., 1998), but effects were significantly larger in the HAT arm (100% of the heroin treatment group used heroin daily at baseline, while 78% had abstained from street-sourced heroin in the past month at the 6-month follow-up). The Spanish

PEPSA trial showed similar results (March et al., 2006), with a significantly greater reduction in frequency of past-month use of street heroin among the supervised injectable heroin group (an average reduction of 16.2 days versus 6.4 days for the oral methadone group). While not in the published results, the Dutch trials and Canadian NAOMI trial also had unpublished data supporting a protective effect of HAT on reducing illicit heroin use (Ferri et al., 2011).

The large German trial (Haasen et al., 2007) defined "treatment responders" as those who showed both a reduction in street heroin use (measured as more than half of 5 urine tests taken in the month prior to the 12-month assessment) and did not show an increase in cocaine use (measured by hair analysis). In their adjusted intent-to-treat analysis where missing data were imputed using the "worst-case" strategy, the heroin-assisted group had nearly twice the odds of reduced illicit drug use (OR = 1.91, 95% CI 1.30-2.79). Per-protocol completer analysis yielded similar results. Based on similar outcome measurements and adjusted intent-to-treat models, the UK RIOTT trial also found significantly higher rates of treatment response among those assigned to injectable heroin relative to those assigned to oral methadone (66% compared to 19%, $p<0.0001$) (Strang et al., 2010). Finally, the Belgian TADAM trials showed significant improvements in street heroin use among the heroin-assisted group (supervised injectable or inhalable) relative to the oral methadone group, improvements that began at the 3-month assessment and persisted through the 12-month assessment.

Four trials specifically assessed illicit use of non-opiate drugs. For most substances, little evidence suggested a relative benefit of HAT relative to methadone. The early UK trial found no evidence of significant effects on non-opiate drug use, which for their sample primarily consisted of barbiturate and amphetamines. The Swiss trial similarly found that changes in daily use of alcohol, tobacco, cannabis, cocaine, and/or barbiturates did not significantly differ across treatment conditions (Perneger et al., 1998). The Belgian TADAM trial reported no significant differences for cocaine or excessive alcohol use (Demaret et al., 2015); and the Canadian NAOMI trial also found no significant changes for frequency of cocaine use across either treatment arm (Oviedo-Joekes et al., 2009a).

However, the two trials that separately assessed benzodiazepine use found significantly larger reductions in use among those in HAT relative to those receiving oral methadone. In the Swiss trial (Perneger et al., 1998), results from 48 participants showed that daily use of benzodiazepines fell from 44% to 0% in the heroin treatment group versus 43% to 33% in the control group (difference $p = 0.049$). Yet, these findings should be interpreted with caution as Swiss trial HAT participants who were dependent on benzodiazepines received clorazepate substitution treatment in addition to their assigned study medication; control group participants were not necessarily offered this additional treatment. Exploratory analysis from the Belgian TADAM found a significantly greater decline in self-reported benzodiazepine use among those receiving supervised injectable or inhalable heroin relative to those receiving oral methadone (Demaret et al., 2015), although the authors note that medical staff in the treatment center targeted

diminishing benzodiazepine use among the experimental group due to risk of overdose from potential interactions with pharmaceutical heroin.

Criminal offenses

Five of the systematic reviews considered criminal activity or criminal offenses as an outcome (Ali et al., 2017; Egli et al., 2009; Ferri et al., 2011; Koehler et al., 2014; Perry et al., 2015). In all, the five reviews spanned eight heroin-assisted treatment RCTs, plus findings from three non-RCT studies – one case-control study, one observational study, and one pre-post study. Four of the reviews concluded that HAT plus optional oral methadone showed significant benefits relative to oral methadone in terms of reducing criminal activities and criminal justice involvement, while one found uncertain effects.

The earliest of the reviews (Egli et al., 2009) pooled estimates across five RCTs of HAT (one unsupervised injectable, four supervised injectable) and found significant benefits of injectable heroin relative to oral methadone or conventional drug treatment for reducing criminal activity. Pooled effect sizes were smaller in magnitude but still significant when the very large effect size from the Swiss trial was excluded from the meta-analysis, indicating 55% lower odds of offending from HAT compared to methadone treatment (p=0.002).

Ferri et al. (2011) examined criminal offenses and incarceration/imprisonment as secondary outcomes. Based on eight RCTS involving 2,007 patients, they concluded that the findings of the single studies supported that HAT provision reduced criminal activity relative to oral methadone. Pooling results of the two studies that reported on incarceration (Haasen et al., 2007; Hartnoll et al., 1980), they estimated a 36% lower relative risk among those in HAT relative to the control (RR = 0.64; 95% CI = 0.51, 0.79).

Koehler et al. (2014) coded standardized effect sizes (Cohen's *d*) for effects on re-offending from six HAT RCTs. Across all trials, estimates favored HAT for reducing likelihood of reoffending. Based on effect sizes calculated within the review, two trials -- the German trial and the Dutch inhalable heroin trial -- showed medium effects ($0.20 < d < 0.50$). The other four trials had large effect sizes ($d>0.50$) as estimated by the authors. Perry et al. (2015) included results on criminal activity from the German RCT comparing supervised injectable heroin plus optional oral methadone to oral methadone (Löbmann, 2007). Outcomes were assessed as a binary variable for whether respondents self-reported criminal activity or had a police-recorded offense. Both the experimental and control conditions showed a significant reduction at 12 months (treatment end) relative to baseline, although the reduction was larger for the HAT (RR = 1.25, 95% CI = 1.03, 1.51). Furthermore, the study found that the significant declines in criminal activity among the HAT group persisted at 24-month follow-up ($p<0.001$), although this was not assessed for the methadone treatment arm.

Ali et al. (2017) presented findings based on a more recent RCT, the Belgian TADAM trial (Demaret et al., 2015), that compared supervised injectable or inhalable heroin to oral methadone. Criminal involvement was defined as at least six self-reported acts perpetrated or

experienced as a victim during the previous month. Self-reported criminal activity data was validated where possible with official records. While those in the experimental condition reported fewer criminal acts and reduced contact with drug users compared to the oral methadone group at 12-month follow-up, differences were not significant. However, it should be noted that the TADAM trial preferentially included participants who had criminal backgrounds, which may have influenced results relative to other trials.

As shown in **Table 10,** criminal offenses or illegal activities were assessed differently across RCTs, with the majority relying on combined evidence from participant self-report and official records (see **Appendix A**). Most studies found some evidence that HAT had larger effects than oral methadone on reducing criminal activity or criminal justice involvement, with analyses by offense type indicating that effects were driven by lower involvement in drug offenses and property crime or damage. There was little indication that HAT produced greater benefits than oral methadone in reducing patient participation in violent crime. However, participation in violent crime was significantly less common than participation in property or drug crimes among the sample populations, so analyses may have been weakly powered to estimate effects for this outcome. Additionally, most studies did not evaluate changes in crime victimization rates among patients; given the relatively high rates of homelessness, lack of social ties, and mental health problems among trial participants, declining involvement with illicit drug markets to obtain heroin among HAT participants may have had benefits of reducing victimization even if there were limited effects on perpetration of violent crimes.

Table 10. Comparison of Heroin-Assisted Treatment to Control Treatment Condition among Source Studies Included in Systematic Reviews, Findings Criminal Offenses

Experimental v Control		Experimental		Control		Findings
Study: Follow-up point	Criminal activity measure	Baseline	Follow-up	Baseline	Follow-up	
Unsupervised injectable heroin v oral methadone						
Early UK trial: 12 months	Crime as source of income, past year	NR	15 / 42	NR	16 / 46	Not stat sig
	Crime a major income source, past year	NR	18 / 42	NR	28 / 46	Not stat sig[a]
	Any arrest over past year	NR	22 / 42	NR	33 / 46	p < 0.05
	Incarceration/imprisonment in past year	NR	8 / 42	NR	15 / 46	p < 0.05
Supervised injectable heroin (+ oral methadone) v other drug treatment						
Swiss trial: 6 months	Charged in past 6 months: Any	20 / 27	5 / 27	7 / 21	12 / 21	p < 0.001
	Drug use/possession	11 / 27	3 / 27	2 / 21	8 / 21	p = 0.008
	Drug dealing	7 / 27	0 / 27	1 / 21	2 / 21	p = 0.067
	Property/theft	7 / 27	1 / 27	2 / 21	5 / 21	p = 0.015

	Aggression	3 / 27	1 / 27	1 / 21	1 / 21	p = 1.00
	Traffic offense	2 / 27	0 / 27	1 / 21	0 / 21	p = 1.00
	Other	3 / 27	0 / 27	0 / 21	3 / 21	p = 0.10
	Commercial sex past 6 months	4 / 27	3 / 27	2 / 21	2 / 21	p = 1.00
Supervised injectable heroin (+ oral methadone) v oral methadone						
Dutch trial: 12 months	Average days illicit activities, past month	Mean difference (HAT – methadone): –5.81 95% CI: [–8.68, –2.94]				p < 0.05
Spain PEPSA: 9 months	Days per month involved in illegal activities: Mean (SD)	11.5 (13.2)	0.6 (1.6)	8.0 (11.0)	4.1 (8.6)	Absolute diff, p=0.096
German trial: 12 months	Self -reported criminal activity, past year:					
	Any	406 / 515	234 / 515	396 / 500	314 / 500	p < 0.05
	Drug offenses	342 / 515	171 / 515	328 / 500	238 / 500	p < 0.05
	Violent crime	92 / 515	53 / 515	100 / 500	70 / 500	Not stat sig
	Property crime/damage	208 / 515	119 / 515	223 / 500	181 / 500	p < 0.05
	Fraud	106 / 515	38 / 515	120 / 500	53/ 500	Not stat sig
	Police-recorded criminal activity, past yr:					
	Any	224 / 419	173 / 419	206 / 406	209 / 406	p < 0.05
	Drug offenses	162 / 419	122 / 419	143 / 406	147 / 406	p < 0.05
	Violent crime	36 / 419	28 / 419	31 / 406	35 / 406	Not stat sig
	Property crime/damage	134 / 419	96 / 419	116 / 406	125 / 406	p < 0.05
	Fraud	22 / 419	18 / 419	24 / 406	25 / 406	Not stat sig
	Any conviction in past year	NR	49.7%	NR	65.9%	p < 0.05
	Any imprisonment in past year	NR	13.8%	NR	23.6%	p < 0.05
NAOMI: 12 months	20%+ reduction in illegal activity (non-drug) & <10% deterioration other scores	NA	1 / 115	NA	6 / 111	Not stat sig
	Illegal activities ASI subscale score	0.37	0.20	0.35	0.18	p = 0.12
Supervised injectable or inhalable heroin (+ oral methadone) v oral methadone						
Belgium TADAM: 12 months	# of acts committed or experienced as a victim during past month	NR	NR	NR	NR	Not stat sig
Supervised inhalable heroin (+ oral methadone) v oral methadone						
Dutch trial: 12 months	Average days illicit activities, past month	Mean difference (HAT – methadone): –4.27 95% CI: [–6.62, –1.92]				p < 0.05

[a]No longer statistically significant once differential pre-trend between oral methadone and HAT group taken into account.

Social and Health Functioning

Four of the nine systematic reviews evaluated evidence for social or health functioning (Ali et al., 2017; Dalsbo et al., 2010; Ferri et al., 2011; Fingleton et al., 2015). The reviews spanned six RCTs in the UK, Switzerland, Spain, Germany, Canada, and Belgium.

Two reviews evaluated social functioning, defined as integration at work and family or other social relationships, based on the same set of RCTs (Dalsbo et al., 2010; Ferri et al., 2011). Since several trials did not report on individual-level outcomes for social functioning, conclusions were based on the findings of the early UK trial comparing unsupervised injectable heroin to oral methadone (Hartnoll et al., 1980), the Swiss trial comparing supervised injectable heroin to other treatments (Perneger et al., 1998), and three studies comparing supervised injectable heroin to oral methadone (Haasen et al., 2007; March et al., 2006; Oviedo-Joekes et al., 2009a). For integration at work, the three studies comparing supervised injectable heroin to oral methadone found improvements for both the experimental and control conditions by treatment end, although only one study (Oviedo-Joekes et al., 2009a) found significantly greater improvement among the HAT group in employment satisfaction ($p=0.02$) and social relations ($p=0.05$) as assessed by the European Addiction Severity Scale Index (ASI) subscale scores. The early UK trial and Swiss trial showed no evidence of significant changes in employment for either treatment condition. For family relationships, there was little evidence showing a significant difference across treatment conditions in any study.

One review (Fingleton et al., 2015) evaluated effects of various opioid substitution treatments on mental health outcomes. The review included results from four RCTs comparing supervised injectable heroin to other treatments. For the Swiss trial (Perneger et al., 1998), with follow-up assessment at 6 months, those receiving supervised injectable heroin showed significant improvements relative to those receiving other conventional drug treatments for mental-health related quality of life (as measured by the SF-36 health survey; difference in SD units = 0.58, 95% CI 0.07-1.10). However, no significant differences were found across a range of other mental health measures, including suicide attempts, severe depression, cognitive problems, or problems controlling violent behavior. At 12-month follow-up, both the German trial and Canadian NAOMI trial found significant improvements in mental health for those receiving supervised injectable heroin relative to those receiving oral methadone (Oviedo-Joekes et al., 2009a; Reimer et al., 2011). At 9-month follow-up, the Spanish PEPSA trial also found significant improvements in mental health measures across both study conditions, but no significant benefit of supervised injectable heroin relative to oral methadone (March et al., 2006).

Finally, the review by Ali et al. (2017) included mental health results from the Belgian TADAM trial comparing supervised injectable or inhalable heroin to oral methadone (Demaret et al., 2015). The trial found significantly greater improvement in the experimental condition on domains of depression and psychoticism as measured by the Symptom Check-List (SCL-90-R; $p=0.002$), although the review did not draw conclusions based on the finding of the one study.

Serious Adverse Events

Three reviews evaluated evidence for the effects of HAT on serious medical adverse events (Dalsbo et al., 2010; Ferri et al., 2011; Strang et al., 2015). Two of these reviews defined serious medical adverse events as those probably or definitely related to the study medication (i.e.,

related to the prescribed pharmaceutical heroin or methadone) and conducted meta-analyses (Ferri et al., 2011; Strang et al., 2015), while the other provided a narrative discussion of all serious adverse events described in the trials (Dalsbo et al., 2010). Findings spanned results of seven RCTs. While these RCTs may have varied slightly in which incidents were reported as serious adverse events (SAEs), they generally included incidents that were life-threatening (including overdoses necessitating treatment with an antagonist), required inpatient hospitalization or prolonged duration of existing hospitalization, or resulted in persistent or significant disability or injury.

SAEs probably or definitely related to the study medication. Evidence from all reviews supports a significantly higher risk of study medication-related adverse events among the heroin treatment arms. Meta-analyses comparing supervised injectable heroin versus oral methadone resulted in risk ratios of 4.99 [95% CI 1.66, 14.99] (Strang et al., 2015) or 13.50 [95% CI 2.55, 71.53] (Ferri et al., 2011), with the higher estimate based on pooled effects that excluded the German and Dutch injectable trials.

The highest relative risk of serious medical adverse events was found in the Canadian NAOMI trials (RR = 47.31 [94% CI, 2.91, 768.63]), where serious adverse events were defined as overdoses related to study diacetylmorphine medication that required treatment with naloxone or any other medical issues judged to be related to the study medication. A total of 29 serious adverse events were judged to be related to the study medications (24 in the heroin treatment group; 5 in the hydromorphone treatment group). The most frequently observed serious adverse events related to HAT were overdoses and seizures, with infections also reported commonly in the hydromorphone treatment arm (Oviedo-Joekes et al., 2009a). All other source studies found higher risk of serious adverse events for supervised injectable heroin relative to oral methadone, although confidence intervals around estimates from individual studies were generally wide. Across studies, serious adverse events commonly resulted from other illicit drug use, such as respiratory depression associated with concurrent use of benzodiazepines (Reimer et al., 2011), potentially reflective of high rates of co-occurring drug use problems among the patient population recruited into the trials.

All SAEs. One review (Ferri et al., 2011) estimated pooled relative risk for SAEs, regardless of their association with the treatment medication. Based on their meta-analysis, the heroin treatment arm remains at elevated risk relate to oral methadone, but the magnitude of the effect size is greatly reduced (RR = 1.61 [95% CI 1.11, 2.33]).

The large German trial (n=1015) reported a total of 315 SAEs among 212 participants over the 12-month trial period. Comparing treatment arms, 24% (18%) of participants receiving HAT (methadone only) experienced an SAE. SAEs were significantly more likely to be possibly, probably, or definitely related to the study medication for those receiving HAT. Adjusting for the longer average treatment length among those receiving supervised injectable heroin, medication-related SAEs occurred about 2.5 times more often among those receiving HAT, with commonly cited SAEs related to respiratory depression and seizure (Haasen et al., 2007). Similarly, the

Canadian NAOMI trial reported a total of 79 SAEs among 54 participants, with nearly two-thirds (65%) occurring in the HAT group, nearly one-quarter (23%) in the oral methadone group, and the remaining 10 events in the smaller pilot hydromorphone group of 25 patients (Oviedo-Joekes et al., 2009a).

The Dutch injectable trial (n=174) reported a total of 18 SAEs among 16 patients. The proportion of patients experiencing at least one SAE did not significantly differ between those receiving HAT or methadone, and none of the SAEs were considered probably or definitely related to the study medication. The study also separately reported on drug overdoses registered during the trial period. Of the five drug overdoses reported (one classified as mild, three as moderate, and one as an SAE), all occurred within the HAT group. Two of the overdoses were classified as being definitely related to co-prescribed heroin but were not of a severity level to be considered an SAE based on the study's protocol (van den Brink and Blanken, 2002).

The Dutch inhalable trial (n=375) reported a total of 40 SAEs among 37 patients, with slightly higher rates of SAE among those receiving HAT. Six drug overdoses were registered, half of which occurred among those receiving oral methadone. All three overdoses occurring in the oral methadone group and one occurring in the HAT group were considered SAEs (van den Brink and Blanken, 2002). In the Spanish PEPSA trial, 14 SAEs occurring among 14 patients were also split evenly across the oral methadone and heroin-assisted treatment arms (March et al., 2006).

UK RIOTT was the only trial to report a higher rate of SAEs among the oral methadone group (Strang et al., 2010). Twenty total SAEs were reported, with nine occurring in the oral methadone group, seven in the supervised injectable heroin group, and four in the injectable methadone group. Of note, there were two overdoses reported in the oral methadone group (one related to antidepressants and the other to acetaminophen); two overdoses in the HAT group (both after diamorphine injection); and one overdose after methadone injection in the injectable methadone group.

While the early UK trial (Hartnoll et al., 1980) did not report on medical adverse events, the authors noted that during the 12-month trial period 21% (11%) of the heroin-assisted (methadone) treatment arm were admitted to a hospital for treatment of physical conditions related to drug use. By contrast, in the Swiss trial (Perneger et al., 1998), four participants in the HAT arm (14.8%) and six in the methadone treatment arm (25%) experienced at least one overdose over the trial period. The study found a significant reduction in overdose prevalence for the heroin treatment arm (i.e., 48% of the experimental group had overdosed at least once in the past 6 months at baseline); however, given the small sample size of the Swiss trial, this reduction did not significantly differ from that observed in the methadone treatment arm.

Mortality

The same three reviews evaluated evidence for effects on mortality (Dalsbo et al., 2010; Ferri et al., 2011; Strang et al., 2015). All three showed an effect that pointed in the direction of a

protective effect of HAT, but the differences between treatment and control groups were not statistically significantly. In a meta-analysis comparing any HAT provision to methadone alone (five RCTs with 1573 participants), Ferri et al. (2011) estimated a risk ratio of 0.78 [95% CI: 0.32, 1.89]. Estimated effect size was similar for meta-analyses comparing supervised injectable heroin plus optional oral methadone to oral methadone alone (RR = 0.65; 95% CI = [0.25 – 1.69]) based on pooling effects across four RCTs with 1,477 participants (Ferri et al., 2011; Strang et al., 2015).

Given the relatively short follow-up period for mortality measurement, there were very few deaths in either the control or treatment groups across all RCTs. Among the source studies assessing mortality at 6 months (Perneger et al., 1998; Strang et al., 2010), neither treatment arm experienced a death, which precludes estimation of relative risk ratios. Among the five other RCTs with mortality assessed at nine or twelve months, eleven deaths occurred across the methadone treatment groups and seven deaths occurred across the heroin treatment groups (Dalsbo et al., 2010). Given the rareness of mortality events over the time periods of assessment, there is a high degree of imprecision in effect size estimates from any given study (see **Table 11**).

Table 11. Mortality Estimates from Source Studies Included in Systematic Reviews

Experimental v control conditions	Included in Review:			Experimental	Control	
Study: Follow-up length	Dalsbo	Ferri	Strang	Events/Total	Events/Total	RR [95% CI]
Unsupervised injectable heroin v oral methadone						
Early UK trial: 12 months	X	X		2 / 44	1 / 52	2.36 [0.22, 25.20]
Supervised injectable heroin (+ oral methadone) v other drug treatment						
Swiss trial: 6 months	X	X	X	0 / 27	0 / 24	Not estimable
Supervised injectable heroin (+ oral methadone) v oral methadone						
Spanish PEPSA: 9 months	X	X	X	0 / 31	1 / 31	0.33 [0.01, 7.88]
German trial: 12 months	X	X	X	5 / 515	7 / 500	0.69 [0.22, 2.17]
Canadian NAOMI: 12 months	X	X	X	0 / 115	1 / 111	0.32 [0.01, 7.82]
UK RIOTT: 6 months	X	X	X	0 / 43	0 / 42	Not estimable
Dutch injectable trial: 12 months	X	X	X	1 / 76	1 / 98	1.29 [0.08, 20.28]
Supervised inhalable heroin (+ oral methadone) v oral methadone						
Dutch inhalable trial: 12 months	X	X		0 / 117	0 / 139	Not estimable

Notes: (+ oral methadone) indicates that oral methadone was offered as an optional supplement to heroin-assisted treatment.

Some source studies reported on cause of death (Haasen et al., 2007; Hartnoll et al., 1980; March et al., 2006; Oviedo-Joekes et al., 2009a). For five deaths in the methadone treatment arm where cause of death was reported, fatalities were related to barbiturate overdose (suicide likely),

overdose from co-administration of cocaine and heroin, opioid overdose, ruptured aneurysm, and reason unknown. For five deaths in the heroin treatment arm where cause of death was reported, fatalities were related to barbiturate overdose (suicide likely), drug overdose of uncertain nature, intoxication with illicit pneumonia, pneumonia and myocarditis complications, and spleen rupture from falling.

Supplementary Evidence on Individual-Level Outcomes

In addition to the systematic reviews and their individual source studies, we identified 30 additional articles that either presented analyses of individual-level outcomes from an RCT not included in the overview of systematic reviews, provided additional analyses from the previously discussed RCTs, or evaluated longer-term follow-up of participants from the heroin-assisted RCTs.

Findings from a more recently implemented RCT

Our literature search identified five additional articles evaluating the individual-level impacts of HAT based on the Study to Assess Longer-term Opioid Medication Effectiveness (SALOME) (Nikoo et al., 2018; Oviedo-Joekes et al., 2017a; Oviedo-Joekes et al., 2016; Oviedo-Joekes et al., 2017b; Palis et al., 2017), a more recent HAT RCT which did not have published results until after the most recent systematic review.

SALOME was a randomized double-blind controlled trial conducted in Vancouver, Canada and designed to evaluate the noninferiority of injectable hydromorphone relative to injectable diacetylmorphine (heroin) for treatment of long-term opioid dependence. Study recruitment occurred between December 2011–December 2013, with participant eligibility requirements similar to those from earlier supervised injectable heroin RCTs. While the trial was planned to enroll 322 participants across two sites (Vancouver, BC and Montréal, Québec), insufficient funding and inability to obtain government approvals led to a cancellation of the proposed Montréal site and reduction in planned sample size (Oviedo-Joekes et al., 2016). A total of 202 participants were enrolled in the trial, with 102 assigned to supervised injectable heroin and 100 assigned to supervised injectable hydromorphone. Both study conditions allowed for flexible doses of oral methadone to be added to participants' treatment regimens, and all participants had access to other on-site services (e.g., registered nurses, social workers, physicians). Treatment duration for stage 1 of the trial was six months, and participants from either group were allowed to transfer to treatment with oral methadone alone or other conventional treatments at any time.

The SALOME trial specified the primary outcome measure as street heroin use, measured by self-report as days of use in the past month (using the ASI) and the proportion of illicit-heroin-positive urinalysis tests at the 6-month assessment point. Given the increasing prevalence of illicit use of other opioids (e.g., hydromorphone) occurring over the study period, self-reported days of illicitly acquired opioids in the past month was included as a co-primary outcome

(Oviedo-Joekes et al., 2016). Intent-to-treat analysis showed a marginally significant benefit of supervised injectable heroin relative to supervised injectable hydromorphone for self-reported illicit heroin use days (-2.34, 90% CI -4.14, -0.52), but non-inferiority of supervised injectable hydromorphone was supported by intent-to-treat and per-protocol analyses for all other primary outcome comparisons.

Secondary outcomes were treatment retention (defined as receipt of injectable medication on 28 of the past 30 days at 6-months based on clinical records); self-reported number of days participated in illegal activities; self-reported crack-cocaine use; and physical and mental health symptoms assessed using the Maudsley Addiction Profile. Treatment retention was approximately 80% in both groups, with no significant difference. There was little evidence of differences between the supervised injectable heroin and supervised injectable hydromorphone groups across all other secondary outcome comparisons (Oviedo-Joekes et al., 2016). Subgroup analyses by gender or by self-identified Indigenous status showed no significant differences in treatment efficacy across primary or secondary outcomes (Oviedo-Joekes et al., 2017b; Palis et al., 2017).

Mortality and adverse events possibly, probably, or definitely related to study medication were also considered (Oviedo-Joekes et al., 2016). Over the 6-month trial period, a total of two deaths occurred, both in the heroin treatment arm and none related to the study medication. There were 353 related adverse events (in 80 participants) reported in the heroin group and 206 adverse events (in 48 participants) reported in the hydromorphone group, with most commonly cited adverse events related to somnolence, post-injection reaction, or injection site pruritus. The risk of an adverse event was significantly lower in the hydromorphone group (RR=0.61, 95% CI 0.49-0.77). A total of 29 serious adverse events related to study medication, primarily seizures and overdose, were reported in 18 participants, with significantly less risk in the hydromorphone arm (RR=0.20, 95% CI 0.06-0.68). These findings were supported by analyses adjusted for differences across groups in daily total dose of treatment and attendance patterns (Oviedo-Joekes et al., 2017a).

Finally, Nikoo et al. (2018) conducted a secondary analysis of participant employment outcomes following stage 2 of the SALOME trial. Stage 2 of the SALOME trial involved randomizing 144 of the initial 202 participants receiving supervised injectable hydromorphone or heroin in stage 1 (for six months) to instead receive oral forms of the medication for the subsequent six months. At any point in the trial, participants could request to be transferred to treatment with oral methadone only. Comparing the four different treatment arms to oral methadone alone, the authors found no significant differences in likelihood of reporting at least one day of paid work (including through informal channels) in the past month at any follow-up assessment point over the 12-month trial duration. Rates of employment and paid work were relatively unchanged over the study period, with employment rates ranging between 3-4%.

Other outcomes

We identified four articles evaluating heroin-assisted RCT evidence for outcomes not previously discussed. Two of these articles reported results from the German trial (Haasen et al., 2009; Karow et al., 2010), one evaluated the Dutch trials (Blanken et al., 2012), and one was an analysis of secondary outcomes from the UK RIOTT study (Metrebian et al., 2015).

Haasen et al. (2009) analyzed the effect of HAT relative to oral methadone among a subset of participants from the German trial who had provided information on alcohol use. Alcohol use was evaluated using three different variables: self-reported information on average alcohol consumption units per day, Addiction Severity Index (ASI) composite scores, and blood tests for carbohydrate-deficient transferrin (CDT), a biological marker of heavy alcohol use. For both CDT and the ASI scores, the HAT group showed significantly greater reduction than the oral methadone group by the end of the trial period. While both groups reported a significant reduction in average daily alcohol consumption, there were no significant differences between HAT and oral methadone in the self-reported measure.

As noted by the authors, the higher efficacy of HAT for decreasing heavy alcohol use may be partially attributable to study participation requirements. The German RCT required that participants be free from alcohol intoxication when receiving the study medication. Given the shorter half-life and hence higher rates of dispensing for supervised injectable heroin (up to three times per day), this requirement may have acted as a behavioral contingency whereby oral methadone participants were required to abstain from alcohol only in the morning for methadone dispensing but heroin-assisted treatment patients may have had to avoid alcohol throughout the day to receive their morning and evening doses while sober. Further evaluation of the relative effectiveness of HAT for reducing frequency and quantity of alcohol consumption may be particularly important for this population given evidence suggesting increasing prevalence of problem alcohol use among patients during methadone treatment (Hall and Strang, 2017).

Another article using results from the German trial evaluated changes in participants' health-related quality of life (HRQOL) from baseline to trial end (Karow et al., 2010). Based on the Modular System for Quality of Life (MSQoL) to assess HRQOL, both groups of participants exhibited significant improvement in HRQOL, with no statistically significant difference with respect to the overall core module score. However, HAT participants (n=483) experienced significantly greater improvement than oral methadone participants (n=455) on the physical health and material satisfaction measures (p=0.01 and 0.07, respectively). For both those receiving HAT and those receiving oral methadone, significantly greater improvement in HRQOL measures occurred in those randomized to receive additional psychosocial care (psychoeducation and individual counselling) versus additional case management plus motivational interviewing.

The Dutch trial article reported on the results of a heroin craving sub-study conducted in two cities (The Hague and Heerlen) as part of the Dutch HAT RCTs (Blanken et al., 2012). As the

craving sub-study was delayed, only a subset of participants from the Dutch RCTs were enrolled, yielding a total of 73 participants (37 receiving oral methadone and 36 receiving supervised injectable or inhalable heroin). Heroin craving was measured by participant self-report on five items of the Obsessive Compulsive Drug Use Scale assessed bimonthly for 10 months beginning at baseline and concluding two months prior to the end of the trial period. Lower scores on the instrument correlated to fewer obsessive thoughts related to heroin craving. While both treatment groups exhibited similar heroin craving at baseline, participants receiving HAT scored significantly lower for heroin craving at all assessment points, with heroin craving showing a sharp drop at the two-month mark and then remaining relatively stable at that lower level for the remainder of follow-up. Overall, heroin craving and frequency of illicit heroin use followed the same general patterns among both HAT and methadone patients. However, since suboptimal doses of methadone have been shown to limit methadone's effectiveness for reducing heroin craving (Fareed et al., 2011), these findings should also be interpreted in the context of the methadone dosage received by the control groups of the Dutch trials, which were on average lower than in many of the other trials.

Craving, which has been shown to predict relapse and treatment dropout, is a complex construct that involves emotional, environmental, neurobiological, and cognitive aspects (Falcato et al., 2015; McHugh et al., 2014). HAT may serve to reduce craving through multiple mechanisms. Studies comparing the acute effects of injectable heroin versus placebo (i.e., saline solution) among patients in the HAT RCTs have shown a significant and immediate effect of heroin injection on reducing stress response, anxiety, emotional excitation, and subjective craving; increasing emotional well-being; and suppressing cortisol levels (Blum et al., 2013; Gerber et al., 2012; Walter et al., 2011). As supported by qualitative research with HAT participants (Blanken et al., 2010b; Groshkova et al., 2013; Oviedo-Joekes et al., 2014b; Romo et al., 2009), the reliable and structured provision of pharmaceutical-grade heroin through the treatment program may have also reduced stress associated with obtaining an uncertain product through the illicit market and may have changed the psychological relationship with heroin use. Reduced involvement with the illicit drug scene among HAT patients may also play a role in reducing exposure to environmental heroin-related cues.

Finally, one more recently published article presented results on secondary outcomes for the UK RIOTT trial (Metrebian et al., 2015). Outcomes, assessed at the six-month trial end, included other substance use (crack/cocaine, benzodiazepines, alcohol), crime, and health and social functioning. All outcomes were self-reported and collected using standard instruments through in-person interviews with participants. Findings showed no differences across treatment groups (supervised injectable heroin, supervised injectable methadone, oral methadone) for any of the broader substance use measures, health and social functioning, or criminal offenses committed. The only significant across-group difference was for money spent on illicit drugs in the past week, where those receiving supervised injectable heroin showed a significantly greater reduction than those receiving oral methadone (£-92.04, 95% CI: £-140.77, £-43.3). Of note, all

treatment groups achieved significant reductions for crime and money spent on illicit drugs; those receiving supervised injectable heroin or methadone experienced significant improvements in physical health, while those receiving oral methadone experienced significant improvements in mental health.

Findings from additional sub-group analyses of RCTs

Three source articles from the overview of systematic reviews focused on sub-group analyses within the HAT RCTs (Eiroa-Orosa et al., 2010b; Nosyk et al., 2010; Oviedo-Joekes et al., 2010c), and our search strategy identified four additional articles. Of the seven articles, one analyzed the Dutch trials (Blanken et al., 2005); three analyzed the Canadian NAOMI trial (Nosyk et al., 2010; Oviedo-Joekes et al., 2010a; Oviedo-Joekes et al., 2010c); and the remainder were analyses of the German trial (Eiroa-Orosa et al., 2010a; Eiroa-Orosa et al., 2010b; Haasen et al., 2010).

The Dutch trial study evaluated patient-level characteristics predictive of treatment response, where treatment response was pre-specified as a dichotomous multi-domain index incorporating improvements in social function, physical health, or mental health without substantive deterioration in other domains (Blanken et al., 2005). Only one baseline characteristic, prior treatment experience, was found to significantly predict differential treatment impact. Specifically, patients with prior experience participating in abstinence-based treatment had significantly higher rates of treatment response to HAT than to oral methadone (60.5% compared to 23.8%), whereas patients without prior experience in abstinence-based treatment showed similar rates of treatment response across both study conditions (39.2% compared to 37.5%).

Subgroup analyses from the Canadian NAOMI trials compared treatment efficacy by baseline motivational status, gender, and Aboriginal race. For subgroup analyses based on motivational status (Nosyk et al., 2010), motivational status was assessed at baseline using a brief measure that classified participants as low, moderate, or high motivational status. Of the 249 trial participants completing the measure, the majority (52%) were classified as high motivational status, with 34% and 15% classified as moderate and low motivational status respectively. When questioned about reasons for participating, the most common reasons given were “free heroin” (47%), “reduce impact of heroin” (40%), and “limit illegal activity” (38%); low-motivation participants were significantly more likely to select “free heroin” or “cash payments” as a primary reason for participation. The greater effectiveness of HAT relative to oral methadone did not significantly differ by baseline motivation status for treatment retention; beneficial effects of high motivational status on treatment response were observed only among clients in the HAT group.

For gender comparisons (Oviedo-Joekes et al., 2010a), 88 (39%) of trial participants across both study sites were female. At baseline, female participants were significantly younger than males and significantly more likely to report receiving money for sex work in the past month and to have ever been the victim of sexual abuse. Females also exhibited higher HIV and Hepatitis C

virus positivity despite similar rates of injection material sharing. While evidence pointed in the direction of slightly lower treatment retention rates for females (64.8% vs. 75.4%), differences were not statistically significant and both genders showed similar benefits of HAT for treatment retention relative to oral methadone. Unlike with males, HAT did not yield significantly higher rates of treatment response than oral methadone for females, driven primarily by limited improvement from HAT on sub-domains of physical health, family relations, employment satisfaction, and health-related quality of life for females. Subgroup analyses from the Vancouver site (n=192) found no significant differences in relative rates of treatment retention or treatment response based on Aboriginal race (Oviedo-Joekes et al., 2010c).

The larger German trial may have had greater statistical power to detect differences across participant population subgroups. Approximately one-fifth (n=204) of German trial participants were female, and as in the NAOMI trial, females were significantly younger. Females had a riskier clinical profile than males, with significantly higher severity of physical health, mental health, and drug use problems as measured by ASI composite scores (Eiroa-Orosa et al., 2010b). Comparing treatment retention and primary treatment outcomes (e.g., illicit drug use, health) for the HAT arm to the oral methadone arm, female participants did not show the relative benefits of HAT as shown among male participants. This may indicate a different clinical risk profile for women who meet the eligibility criteria to participate in HAT that is less responsive to the specific needs addressed by HAT. For instance, women in the German trial had significantly higher cocaine use frequency than men at baseline; because HAT and oral methadone did not differentially impact cocaine use (for either gender), the relative benefits for the primary outcome of illicit drug use were muted. Relatively high rates of prostitution among the female sample (30% at baseline) may also be a mediating factor in determining treatment efficacy.

Another analysis of outcomes from the German trial compared treatment effectiveness by benzodiazepine use (Eiroa-Orosa et al., 2010a). At baseline, 736 (72.5%) participants reported past-month use of benzodiazepines and/or had positive urinalysis results for benzodiazepines. Relative to other participants, benzodiazepine users had a riskier clinical profile (based on ASI scores) for drug use, economic situation, legal problems, health, and social functioning. While benzodiazepine users were less responsive to both treatment modalities, the greater treatment effectiveness of HAT relative to oral methadone observed in the full sample was not negatively impacted by benzodiazepine use at baseline. However, the significantly lower 12-month treatment retention rates among baseline benzodiazepine users (OR=0.727; 95% CI: 0.550, 0.961) was driven by their significantly lower treatment retention rates in the HAT arm of the study.

While not the study's focus, the German study (Eiroa-Orosa et al., 2010a) also found that HAT participants exhibited significantly greater reductions in benzodiazepine use compared to oral methadone participants. Over the 12-month treatment period, an average of 52.3% and 60.3% of urinalysis tests were positive for benzodiazepines among the HAT and oral methadone groups, respectively, despite similar baseline rates of benzodiazepine use. However, these

differences were small and statistically insignificant when restricting the sample to those participants reporting baseline benzodiazepine use (64.3% and 65.9% positive among HAT and oral methadone, respectively). Thus, differential rates of benzodiazepine use across treatment arms may reflect differential willingness of providers to prescribe benzodiazepines to patients depending on the treatment arm in which they were enrolled (e.g., program doctors may have been less likely to prescribe benzodiazepines to HAT patients given concerns regarding adverse events).

Unlike most other RCTs, the German trial did not restrict participant eligibility to require previous attempts with maintenance treatments. Instead, participants were required to have had two prior treatment attempts in any form of substance use treatment, including inpatient or outpatient abstinence-based programs. This difference in eligibility criteria allowed for analyses of whether there were differences in treatment efficacy for participants with no previous maintenance treatment experience (Haasen et al., 2010). Compared to other participants, patients with no previous maintenance treatment experience had a substantively and significantly more severe profile in terms of frequency of heroin use and frequency of injected drug use in the past month, but a significantly shorter lifetime duration of heroin use. Relative to other participants, those without previous maintenance experience had a significantly greater response from HAT for reducing illicit drug use but did not exhibit significantly greater improvements in health.

Longer-term follow-up of HAT recipients

We identified eight articles evaluating outcomes for HAT participants following the conclusion of the trials. One article followed up on medication use patterns among participants from the Swiss trial (Perneger et al., 2000). One article evaluated four-year treatment retention and treatment response among 149 participants offered HAT through the Dutch trials (Blanken et al., 2010a). One article conducted a two-year follow-up of illicit drug use, HIV risk behavior, mental health, and physical health among participants from the Spanish PEPSA trial (Oviedo-Joekes et al., 2010d). One article evaluated treatment response three months following treatment discontinuation of the Belgian TADAM trial (Demaret et al., 2016), and one explored two-year outcomes for a non-randomized component of the Canadian NAOMI trial (Oviedo-Joekes et al., 2014a). Three articles assessed two-year outcomes for individuals from the German trial (Soyka et al., 2011; Verthein et al., 2008; Verthein et al., 2011). Only one identified article adopted an RCT design (Demaret et al., 2016).

RCT Evidence. Demaret et al. (2016) conducted a follow-up study of the 12-month Belgian TADAM trial to examine the extent to which treatment benefits persisted following discontinuation of HAT. At the end of the trial period, patients in the experimental condition receiving supervised injectable or inhalable heroin were offered an alternative treatment. Participants in the control condition of oral methadone were allowed to continue treatment or transfer to an alternative treatment. Illicit heroin use, cocaine use, criminal involvement, and mental and physical health were assessed three months after treatment discontinuation. Illicit

heroin and cocaine use were measured through self-report and urinalysis; criminal involvement was measured by self-reported criminal activity or victimization; and mental and physical health were assessed using standard instruments (SCL-90-R and MAP-HSS, respectively). Follow-up assessment included 61 trial participants, 31 from the HAT group and 30 from the oral methadone group.

While participants receiving HAT had shown a significant reduction in illicit heroin use relative to participants receiving oral methadone at the end of the trial, three months following HAT discontinuation participants showed a significant increase in illicit heroin use such that there were no longer differences with the oral methadone condition. However, illicit heroin use for both groups remained significantly lower than at baseline. There were no significant differences between groups at follow-up for cocaine use, criminal involvement, or mental health; however, there had been no significant differences for these outcomes during the trial period. These results would be consistent with HAT being superior to oral methadone specifically at suppressing illicit heroin use but only during the course of HAT itself.

Evidence from follow-up cohort studies of RCT participants. Several cohort studies have assessed longer term outcomes among participants from earlier RCTs. Here, we review findings from seven identified articles spanning five of the HAT RCTs. Given the design of these studies, findings should be interpreted as descriptive or correlational and not necessarily causal. Our discussion is thus not focused on the effectiveness of HAT relative to conventional drug treatments such as methadone, but is rather intended to provide a descriptive overview of how outcomes evolved for trial participants following the conclusion of the trial period.

Perneger et al. (2000) conducted a follow-up assessment of opiate use patterns among participants from the Swiss trial up to 30 months after entry into HAT. Of the 37 patients eventually placed in HAT, ten (27%) had switched to oral methadone or detox treatment. Accounting for days of treatment received, the authors estimated this translated to one "successful" treatment transition per 6 patient-years. Over the entire 30-month period, about half of patient-days corresponded to combined use of prescribed injectable heroin and oral opiates (methadone or morphine), about 40% corresponded to use of prescribed injectable heroin alone, and about 7% corresponded to use of oral methadone alone.

Following the conclusion of the 12-month Dutch RCT treatment period, study protocol stipulated that those receiving HAT would cease treatment for at least two months; participants who exhibited substantial deterioration during this follow-up were allowed to re-enroll in HAT for an unspecified period of time. During the two-month discontinuation period, 82% of those classified as "treatment responders" from HAT had shown significant deterioration such that the multi-domain outcome index measuring treatment response had returned to baseline levels. However, it is unclear whether this finding reflects the importance of remaining on HAT to retain treatment benefits, participant behavioral or reporting responses driven by the knowledge that deterioration would result in HAT, or an adjustment period whereby participants transitioned to an inadequate dose of an alternative treatment medication. Blanken et al. (2010a) conducted

an observational cohort study to evaluate four-year outcomes for 149 participants eligible to continue HAT following the Dutch trial conclusion. Treatment retention at four years was 55.7% (95% CI = 47.6, 63.8), with the majority of discontinuations attributable to insufficient treatment response and administrative discharge for rule violations, primarily due to attempts to divert prescribed heroin outside the treatment center. Of those who discontinued HAT, nearly 85% were in some form of treatment, mainly methadone treatment. Those who remained in HAT at four-year follow-up exhibited significantly greater health improvement than those who discontinued, which likely reflects selection effects.

Following the conclusion of the nine-month PEPSA trial in Andalusia, Spain, all 23 participants who had been randomized to the supervised injectable heroin arm continued receiving it from the clinic under the protection of Spain's compassionate use law. Additionally, treatment completers who had been randomized to the oral methadone group were offered the option of switching to supervised injectable heroin after the trial end; 13 (61.9%) of the 21 eligible oral methadone participants elected this option. In a follow-up cohort study of the participants from this trial, Oviedo-Joekes et al. (2010d) compared outcomes across current HAT recipients, former HAT recipients, and those who had never received HAT. Changes were assessed between baseline (prior to randomization) and at two-years after the trial's conclusion.

For the 54 participants with follow-up data (of the 62 original trial participants, three had died, three were unreachable, and two were incarcerated outside of Andalusia), 44% were continuing to receive HAT, 46.3% were receiving oral methadone, 5.6% reported no longer using drugs, and 3.7% were not receiving any form of treatment. From baseline to two-year follow-up, all three groups (current HAT, former HAT, never HAT) experienced significant reductions in illicit heroin use, with those currently receiving HAT reporting significantly less frequent illicit heroin use than the other two groups at follow-up. Declines in cannabis use, binge drinking, and HIV risk behavior reported by current or former HAT recipients were not observed for those who had never received HAT. Finally, those continuing to receive HAT exhibited significantly greater improvements in mental health scores (SF12) and ASI psychiatric composite scores than those no longer receiving HAT.

As noted in the overview of systematic reviews for treatment retention, a relatively higher percentage of individuals assigned to supervised injectable heroin or hydromorphone in the Canadian NAOMI trial voluntarily transferred to oral methadone during the course of the 12-month trial. Oviedo-Joekes et al. (2014a) conducted a follow-up assessment 12 months after trial end comparing treatment retention and illicit heroin use on an intent-to-treat basis, with subgroup analysis comparing those who had voluntarily transitioned to oral methadone to those who were involuntarily transitioned off of injectables due to trial end. Despite higher treatment retention (defined as engagement in treatment or abstinence from illicit heroin use) in the HAT group at the 12-month trial end, by the 24-month follow-up there were no longer significant differences between the HAT and oral methadone groups. Among those assigned to supervised injectable treatment, comparisons of those who voluntarily versus involuntarily transitioned showed those

who voluntarily switched to oral methadone had significantly higher treatment retention (AOR = 5.55; 95% CI: 1.11, 27.81) and marginally significant lower illicit heroin use days in the past month (-5.58; 95% CI: -11.62, 0.47) at 24-month follow-up.

Finally, three articles conducted two-year follow-up studies of participants randomized to supervised injectable heroin or oral methadone within the German trial. In the German trial, after the initial phase of 12-months treatment with HAT or methadone, patients who completed HAT were allowed to continue treatment for another 12 months; patients who completed methadone treatment and exhibited "unsatisfactory" clinical progress as determined by doctors' assessment were allowed to switch to HAT for 12 months. Of the first phase treatment completers, 99.4% (344/346) of the HAT group elected to continue treatment, and 40% (90/200) of the methadone treatment group were transferred to HAT (Verthein et al., 2011).

Verthein et al. (2008)'s prospective cohort study followed participants assigned to the HAT group for a two-year period. Of the 515 participants initially randomized to HAT, 54.8% were still receiving HAT after 24 months. The majority of dropout was due to participants switching to other medication treatment (27.1%) or abstinence treatment (9.3%); incarceration (16.0%); or theft/diversion of prescribed heroin (7.6%). Analyses of the methadone-HAT switching group (Verthein et al., 2011) showed a similarly high proportion of dropouts during HAT receipt related to uptake of conventional maintenance treatment (38.9%) or abstinence-based treatment (11.1%), and lower rates of dropout due to imprisonment (5.6%). During the second study phase, the methadone-HAT switching group showed improvements in physical health and drug use such that they "caught up" with the two-year HAT group by the end of the second trial phase. However, by definition, the methadone-HAT switching group members were negatively selected from the original methadone group; patients who did well on methadone during the first trial phase were automatically excluded from the trial's second phase. Thus, while this evidence may support the efficacy of HAT for opioid-dependent patients who do not respond to oral methadone, the study does not provide causal evidence on how longer-term HAT compares to longer-term methadone for the initial RCT target population.

Soyka et al. (2011) recruited a subset of patients receiving long-term HAT (n=20) as part of the second phase of the German HAT RCT in order to compare their cognitive functioning to that of methadone (n=24) or buprenorphine (n=22) patients participating in a separate RCT. Cognitive performance was assessed using a standardized instrument (the Act and React Test System) that measures neuropsychological functions related to driving ability, including reactivity, visual perception, and stress tolerance. While the HAT group performed significantly worse on some tests (attention under monotony and reactivity under stress conditions), other tests showed limited differences. However, as patients were recruited from different RCTs with different participant eligibility requirements, these findings may reflect baseline differences (e.g., HAT patients have longer histories of dependence) as opposed to causal effects of the treatment.

Evidence from other cohort studies. We identified eight additional cohort studies that evaluated the long-term outcomes of individuals receiving HAT – one in the UK context and

seven in the Swiss context. The sample population from these studies are not drawn from RCTs, instead drawing on information from countries where HAT is a legally available treatment for heroin dependence. Given the absence of a comparison group, we focus discussion primarily on providing descriptive evidence of long-term outcomes for HAT participants recruited outside of an RCT setting.

In the UK, heroin prescription for treatment of opioid dependence has been available since the early 1920s, though since 1968 physicians must obtain a special license to prescribe this treatment. Metrebian et al. (2006) reviewed patient case notes from 27 of the 42 UK clinics providing HAT in 2000 in order to assess treatment patterns and characteristics among individuals receiving a heroin prescription. Of the 210 patients evaluated, the vast majority of patients were receiving HAT for take-home administration (88%) and in injectable formulation (88%), but daily doses ranged widely (median = 200 mg; range = 10-900 mg). The length of HAT receipt ranged from a few months to 36 years, with a median treatment length of six years. When followed up with two years later in 2002, most participants (70%) were still receiving HAT and just over 10% had transferred to an oral maintenance treatment or become abstinent.

In Switzerland, the Medical Prescription of Narcotics Programme (PROVE) was an experimental prospective cohort study conducted from 1994 to 1996 that accepted admission of 1,035 individuals into a treatment program offering prescribed heroin, methadone, and morphine plus an intensive suite of social services. Participants were at least 18 years old, had at least two years of heroin dependence, had at least two prior treatment episodes, and experienced health or social problems as a result of their heroin use. Beginning in 1998, a new decree allowed HAT centers to admit new patients beyond the initial experimental cohort. We identified one study of Swiss HAT participant outcomes up to 2.5 years after enrollment (Steffen et al., 2001); five articles studying outcomes from 4 to 7 years after enrollment (Guttinger et al., 2003; Rehm et al., 2005; Rehm et al., 2001; Ribeaud, 2004; Sendi et al., 2003); and one article with follow-up data more than ten years post-enrollment (Frick et al., 2010).

Steffen et al. (2001) evaluated trends in seroprevalence among 1,035 individuals enrolled in the 1994 to 1996 PROVE cohort from baseline to 30 months post-enrollment. Baseline rates of seroprevalence for human immunodeficiency virus (HIV; 15%), hepatitis B (HBV; 73%), and hepatitis C (HCV; 82%) were high among participants, similar to the high rates observed among HAT RCT participants. Most participants experienced viral co-infections (Sendi et al., 2003). Risk for HBC and HCV infection dropped by nearly 50% after the first six months of treatment and persisted at this lower level up to 30 months after treatment entry, paralleling a decline in self-reported needle sharing behavior from 16% to 5%.

Ribeaud (2004) evaluated long-term trends in criminal justice involvement for a sample of 882 HAT patients who entered the PROVE trials between January 1994 and July 1996 and were alive four years after HAT admission. For the 426 patients (48%) who remained in the program all four years, police records showed the prevalence (incidence) rates of offenses unrelated to heroin use/possession significantly declined from 54% to 31.5% (1.86 to 0.73) from the year

before to the year after treatment, with a slower rate of decline through the fourth year of treatment. These effects are seen across drug and property offense types, with the largest effects for shoplifting and cocaine use/possession. Incidence rates related to heroin use/possession also declined significantly, falling from 1.2 the year before treatment to about 0.05 one year post-treatment. Individuals who left the HAT program before four years experienced similar declines in offense rates over the four-year period, with one exception. The group who left HAT before one year experienced a much slower and smaller decline in incidence rates; however, this appeared to be driven by a few outliers.

Similar crime drops between those who remained in HAT and those who discontinued treatment may be related to the fact that many who left HAT transferred to alternative treatment regimes. Regardless of time to treatment discontinuation, approximately 60% of patients who left transferred to methadone or abstinence-based treatment. Among those who dropped out before one year of HAT, 43.2% enrolled in methadone and 21.1% in abstinence-based treatment. Dropout seemed to cluster within the first year of treatment, a finding also borne out in another Swiss study with follow-up assessed up to 14 years after initial HAT entry (Frick et al., 2010).

Guttinger et al. (2003) evaluated six-year outcomes from the first cohort of individuals who entered into PROVE between January 1994 and March 1995 (n=366). Of those clients who were still alive (88.2%), 148 were still in or had reentered HAT (mean cumulative length of stay in HAT of 6.1 years), while 175 had left HAT in the evaluation period without re-entering (mean length of stay 2.4 years). While it was unknown how many individuals had entered an alternative treatment program, the most common self-reported reasons for discharge were problems with adherence to treatment protocol (30.6%), transfer to abstinence-oriented treatment (24.3%), or transfer into methadone treatment (21.6%); these rates are comparable to those from a larger PROVE cohort study (Rehm et al., 2001). Interestingly, comparing outcomes from baseline to 6-year follow-up showed no significant improvement in employment for those currently or previously receiving HAT; those clients still receiving HAT actually experienced a significant increase in dependence on social benefits (19.1% to 39.7%). There were also no significant changes from baseline in social integration outcomes, despite significant declines in (near) daily use of heroin.

Rehm et al. (2005) examined deaths during HAT treatment among clients in Switzerland over the seven-year period from 1994 to 2000. The time in treatment was defined as admission through the month after discharge. Using this definition, their time period covered just over 4600 person-years in treatment and 49 deaths, yielding a crude rate of 0.011 deaths per person-year. This is a substantially higher mortality risk than sex- and age-adjusted rates in the general population; but it is substantially lower than mortality risk estimates based on other opioid-using populations. Examining cause of death, over one-third of deaths were due to AIDS or HIV-related outcomes; nearly two-fifths were from accidents; 16.3% and 10.2% were from suicide and intoxication/overdoses, respectively.

Add-on interventions

Finally, we identified one study of the German RCT examining whether psychosocial treatment independently contributed to the efficacy of HAT or methadone; and two recent studies that evaluated add-on interventions for HAT.

As noted in **Table 4,** the German RCT had a 2x2 randomization design, crossing HAT and oral methadone with two psychosocial treatment modalities: psychoeducation plus drug counselling vs. case management plus motivational interviewing. One article evaluated differential outcomes based on assignment to the psychosocial intervention conditions (Kuhn et al., 2007). No differential effects of psychosocial treatments were significant for health status or illicit drug use outcomes.

One recent RCT evaluated contingency management targeting cocaine use as an add-on intervention for participants enrolled in supervised HAT in 12 addiction treatment centers in the Netherlands (Blanken et al., 2016). In addition to meeting the eligibility requirements to receive supervised injectable or inhalable heroin, participants had to report at least four days of cocaine use in the past month. Participants were recruited between April 2006 and January 2010 and randomized to receive supervised HAT plus contingency management (n=107) or supervised HAT alone (n=107). Treatment retention rates at six months were similar across groups (90-93%) with no significant difference across groups in the multi-domain measure of treatment response. However, those randomized to receive add-on contingency management achieved significantly longer duration of abstinence from cocaine use as assessed by multiple measures.

One pilot RCT study evaluated the effects of adding an exercise intervention to HAT (Colledge et al., 2017). Participants were recruited from a HAT facility in Basel, Switzerland at the end of 2014 and randomized to receive usual care plus 12 weeks of exercise therapy or usual care plus 12 weeks of non-exercise activities. Just under half of individuals invited to participate in the study gave consent. Compliance with study protocol was significantly higher in the experimental condition, and those receiving the exercise intervention showed a significant increase in time spent exercising at high-intensity level relative to those in the control condition. Few significant differences across groups were observed in any other outcome, including substance use and psychological assessments.

Summary of Findings for Individual-Level Outcomes

HAT versus oral methadone. Evidence from all studies indicates that HAT has benefits relative to oral methadone only across several domains, with the strongest and most consistent effects found for improving treatment retention and reducing illicit heroin use. All but the Dutch trials found higher relative treatment retention rates among the HAT group, although differences were not significant for the relatively small Swiss (n=51), Spanish (n=62), or Belgian (n=74) RCTs. Across all RCTs, treatment retention rates over the 6 or 12 months of the trials among the HAT groups are relatively high, ranging from 67% to over 90%. As noted previously, findings

for HAT versus oral methadone should largely be viewed as evidence of the relative efficacy of offering supervised injectable HAT and/or oral methadone compared to offering oral methadone alone for a patient population that has previously attempted oral methadone but continued to use heroin regularly.

In this context of an eligible patient population that has largely (though not in all cases) exhibited challenges in being retained or responding to oral methadone, an important component of HAT's relative benefit for treatment retention stems from participants disengaging with treatment service immediately upon being assigned to oral methadone. Additionally, the benefits for treatment retention may in part derive from asymmetry in defining retention as retention in "any treatment" since HAT participants can (and do) switch to methadone but the converse is not permitted. Combined with evidence that shows a not insubstantial share of HAT discontinuers transfer to oral methadone, provision of HAT may be viewed as a potentially effective strategy for engaging and stabilizing a difficult-to-treat population before transitioning them to alternative or more conventional forms of treatment.

However, it is worth noting that many of the HAT RCTs reported serious challenges with recruiting participants. For instance, while the recent Belgian TADAM trial planned to enroll 200 participants, only 74 participants (less than 40% of the expected number) were enrolled in the trial (Demaret et al., 2015). Follow-up interviews with those refusing trial entry revealed a variety of reasons for refusal, including concerns over the limited 12-month duration of the trial, a desire to reduce or cease use of heroin, fear exacerbating their reliance on heroin, and concerns over the treatment center's location in proximity to a police station (Demaret et al., 2014). Other trials have reported similar problems with recruitment (Gartry et al., 2009; Strang et al., 2010), and in countries where HAT is available on a non-experimental basis (e.g., Switzerland, Netherlands) take-up remains relatively low (Uchtenhagen, 2017). Difficulties with recruitment may mitigate some concerns that heroin users will "abuse" or "take advantage of" the offer of prescribed pharmaceutical-grade heroin; yet it also highlights the significant challenge of attracting some individuals with chronic opioid use disorder into treatment. Recruitment challenges are not insurmountable, however, and the most recent heroin-assisted treatment SALOME trial in Canada (comparing injectable heroin to injectable hydromorphone) actually received more applicants than could be randomized into a trial condition (Oviedo-Joekes et al., 2015).

With regard to illicit heroin use, the evidence is strong and consistent in showing that, among patients with heroin dependence who have not responded to conventional treatments (most commonly oral methadone), *supervised* injectable HAT results in significantly greater reductions in illicit heroin use than oral methadone. While studies used different outcome definitions and assessment methods, all showed significantly greater reductions in illicit heroin use outcomes among the HAT trial arms. Findings from all trials also indicated that the large and significant reductions in illicit heroin use among the HAT groups occurred shortly after beginning HAT, and these lower levels of illicit heroin use persisted through the duration of the trial. There is

some evidence suggesting that these benefits persist only during the course of the treatment, with several studies showing that use of illicit heroin reverts to pre-treatment levels following forced discontinuation of HAT. Thus, while HAT demonstrates clear benefits in shifting heroin users away from the illicit market, more work may be needed to understand how to best implement HAT as a longer-term treatment option; whether there is an optimal duration of HAT whereby patients can be transitioned to other treatment modalities while maintaining benefits of reduced illicit heroin use; and how patient expectations and perspectives can be integrated in order to improve treatment implementation (Rehm et al., 2001; Vogel et al., 2017).

Because most trials did not provide sufficient information to calculate how average baseline illicit opioid dose per day compared to within-trial total opioid dose per day, it is unclear whether HAT participants significantly reduced total opiate consumption relative to oral methadone participants; regardless, however, it seems that HAT provision offers this group of individuals a safer, more consistent, and more reliable opioid source than those available through illicit market channels. The observed benefits of HAT for illicit heroin use reduction may in part be due to pharmaceutical heroin's relative benefits for reducing heroin craving among the set of individuals who have failed to respond to methadone.

Evidence also supports that HAT is superior to oral methadone for reducing criminal activity among people with chronic treatment-refractory heroin dependence. The majority of RCTs that reported on criminal activity as an outcome found that participants receiving HAT exhibited significantly lower involvement in illegal activities and lower likelihood of formal criminal justice involvement (e.g., arrest, charge, incarceration) than those receiving oral methadone. These effects are primarily driven by a larger decline in drug offenses and property crime/damage among those receiving HAT, which is consistent with their reduced street heroin use leading to less reliance on illicit channels to obtain or pay for heroin. No study found a significant benefit of HAT relative to oral methadone for reducing violent crime. However, the relative benefits of HAT versus oral methadone for reduced criminal activity have been less marked in the most recent RCTs. The UK RIOTT, Canadian NAOMI, and Belgian TADAM trials all found that treatment was associated with significantly reduced criminal involvement, but with no significant differences across the HAT and oral methadone trial arms. Given the clinical profile of eligible trial participants and their prior treatment histories with oral methadone, it is particularly surprising that such significant benefits were achieved for individuals randomized to the methadone control conditions in these trials.

The evidence for other outcomes is more limited. The evidence base does not support a significant difference between HAT and oral methadone with respect to use of cocaine. The evidence base also does not support a significant difference with respect to alcohol, tobacco, or cannabis; although these outcomes were often not considered in trial evaluations. However, some evidence suggests that HAT has greater benefit than oral methadone for reducing illicit use of benzodiazepines. While one trial (UK RIOTT) found no significant differences for changes in benzodiazepine use across trial arms, three RCTs (Swiss, German, Belgian) found significantly

greater reductions among HAT relative to oral methadone treatment participants. However, attributing these effects to the provision of HAT confounds the possibility that trial staff paid greater attention to reducing benzodiazepine use among participants who were receiving HAT given the elevated risk of overdose from concurrent use of opioids and sedatives.

Studies assessed changes in mental and physical health using a variety of measures, including dichotomous composite indexes that precluded distinguishing physical from mental health factors. Generally, trials showed significant improvements in physical and/or mental health for those randomized to HAT, although these effects were often not significantly different from those observed among participants randomized to oral methadone treatment. While the evidence base does not overwhelming support higher efficacy of supervised HAT compared to oral methadone treatment for improving health outcomes among patients who have previously not responded to conventional treatment modalities (primarily methadone), most trials showed significant improvements in at least one of these domains for participants randomized to HAT as well as for participants randomized to oral methadone treatment. Relative improvements among HAT participants appear to be more marked in trials that required participants to have multiple prior attempts with medication treatments.

Finally, the evidence does not support a significant difference between HAT and oral methadone with respect to social functioning or mortality. Most trials found significant improvements in some measures of social functioning (e.g., housing situation, social relations) for both the HAT and methadone treatment trial conditions, with little evidence showing a significant difference across groups. Despite access to social, legal, and employment services in most trials, participants in both forms of treatment showed little improvement for labor market outcomes. It is unclear the extent to which multiple visits per day to receive prescribed heroin creates a barrier for improvements in certain aspects of social functioning. However, given the particularly severe clinical profile of most patients and the relatively short duration of the trials (up to 12 months), a longer follow-up duration may be required to detect differences in these outcomes.

The finding of insignificant differences between HAT and oral methadone treatment for mortality should be considered in light of the rarity of fatal incidents occurring across either the HAT or oral methadone participants with the context of the relatively short trial periods. Longer-term follow-up from prospective cohort studies supports that those receiving HAT have improved mortality relative to status quo, but it is unknown how mortality outcomes compare between HAT patients versus patients in other forms of treatment for heroin dependence.

Any relative benefits of HAT must be considered in light of strong evidence indicating that HAT carries significantly greater risk than oral methadone for serious adverse events, including seizures and overdose. However, because of the supervised nature of the medication administration and subsequent monitoring of patients within most RCTs, the majority of SAEs related to supervised injectable heroin were managed quickly and clinically, potentially mitigating more serious consequences such as death. Thus, while injectable HAT may carry

greater risk of adverse events than oral methadone, the delivery of pharmaceutical heroin within a supervised healthcare setting likely carries lower risk of adverse events than use of heroin within the illicit market context.

Injectable heroin versus injectable methadone. The evidence for the relative effectiveness of supervised injectable heroin relative to supervised injectable methadone stems from only one trial (UK RIOTT). While participants receiving HAT were significantly more likely than those receiving injectable methadone to meet the trial definition of "treatment response" (i.e., 50 percent or more negative urinalysis specimens in the final three months of the six-month trial), the two trial arms did not significantly differ across most other outcomes. However, according to the study authors, the UK RIOTT trial was not designed to have adequate power to detect differences between the injectable arms and thus the absence of statistically significant differences may be more reflective of effect size imprecision than a true null.

Injectable heroin versus injectable hydromorphone. The recent Canadian SALOME trial suggests that, when offered with optional flexible doses of oral methadone, supervised injectable hydromorphone may be as effective as supervised injectable heroin for improving patient-level outcomes. Based on the findings from this one RCT involving 202 patients, injectable hydromorphone has similar effectiveness as injectable HAT with respect to treatment retention, street opioid use, illegal activities, as well as physical and psychological health. Additionally, over the 6-month trial period, supervised injectable hydromorphone resulted in significantly fewer serious adverse events and serious adverse events specifically related to the study medication.

The observed noninferiority of supervised injectable hydromorphone may suggest the importance of route of administration for engaging in treatment this subset of patients who have not responded to conventional oral medication treatments. Indeed, based on the pilot arm of the NAOMI trial, Marchand et al. (2011) found similar rates of client satisfaction among participants receiving injectable hydromorphone or injectable heroin, satisfaction levels which significantly exceeded those expressed by the oral methadone treatment group.

5. Results for Effects of Heroin-Assisted Treatment on Community-Level Outcomes

Prior research has demonstrated several challenges with implementing HAT, including concerns about the potential impacts of HAT on local communities. In Australia, a HAT feasibility study consulted with treatment providers, police, current and former drug users, and heroin prescription opponents to identify concerns associated with implementing the trial (Bammer et al., 2003). These included an influx of heroin users into the neighborhood (i.e., "honeypot effect"), diversion of study medication to illicit markets, greater perceived acceptability of heroin use, compromised traffic safety due to increased driving while under the influence of heroin, and increased public disorder or violent crime.

Similar concerns about diversion and public safety have created challenges and additional costs for locating study sites and constructing security systems (Gartry et al., 2009; Oviedo-Joekes et al., 2009b); have been expressed by staff participating in trials across multiple settings (Demaret et al., 2012); and have been voiced by local community stakeholders (Miller et al., 2010; Uchtenhagen, 2010). Alternatively, others have viewed the significant reductions in criminal activity among HAT participants as evidence that the programs may reduce community-level crime and heroin use by removing user-dealers from the illicit market and potentially reducing the recruitment of new users into the market (Killias, 2000).

Our search strategy yielded five studies that evaluated the extent to which the implementation of HAT impacts certain community-level outcomes. No study used an RCT design, which is unsurprising given the unit of randomization across all HAT RCTs has been the individual and not the community. However, all studies leveraged the timing of the implementation of a HAT RCT to conduct pre-post assessments of changes in local outcomes. Two studies were conducted in the context of the Canadian NAOMI trials (Ally et al., 2011; Lasnier et al., 2010); two in the context of the UK RIOTT trial (Miller et al., 2010; Miller et al., 2011); and one in the Dutch trial setting (van den Brink and Blanken, 2002). All studies employed a pre-post design or provided descriptive evidence based on participant incidents within a heroin-assisted RCT, with no study including a comparison group.

The two Canadian NAOMI trial studies used interrupted time series analyses to assess how the opening of the clinics influenced public order and public safety outcomes. (Lasnier et al., 2010) used autoregression modeling to separately examine how the opening of the NAOMI clinics in Montreal (June 2005) and Vancouver (April 2005) influenced rates of crime and public disorder. Crime was operationalized as the weekly or monthly number of crimes (violent, property, drug-related) reported in police data within the Plateau Mont-Royal district area around the Montreal clinic or within the Downtown Eastside area around the Vancouver site. Public disorder was similarly operationalized as the weekly or monthly number of calls for service

related to disorderly conduct, public nuisance, misbehavior, vagrancy, or panhandling. The authors considered effects based on a binary variable for whether the clinic was open or a continuous measure of the number of enrolled NAOMI participants, and all regressions controlled for average temperature and precipitation. No clear patterns emerge from their results, and estimated effects are largely small and insignificant. However, the absence of pre-period data (less than one year) for the Vancouver case study may limit the credibility of their findings for that site, and the small number of patients enrolled in the NAOMI sites (52 in Montreal and 158 in Vancouver) may greatly limit statistical power to detect neighborhood-level effects. Thus, this may be a weak null effect.

Ally et al. (2011) combined an autoregression modeling approach and ethnographic walks within a 200-meter radius of the NAOMI clinic in Montreal to assess how the opening of the clinic impacted: 1) volume of injection debris; 2) volume of other street debris (e.g., drugs, condoms); 3) disorderly behavior, such as public drug consumption or prostitution; 4) bottles of alcohol. They found the opening of the clinic significantly reduced the volume of injection and other street debris around the clinic but had no effect on disorderly behavior or alcohol bottle debris. Results were similar when they replaced the binary indicator for study site opening with a continuous measure for number of patients. The authors found a significant association between the number of participants and injection or street debris; for every additional enrolled patient, volume of injection debris reduced by about 3.3 units ($p<0.01$) and street debris by about 0.61 units ($p<0.05$). While this suggests a potentially beneficial effect of the HAT facility for reducing public disorder, a stronger causal argument could be made with the inclusion of a comparison area or alternative data collection strategies.

Miller et al. (2010) interviewed key informants from the community before and after one of the UK RIOTT treatment centers opened in South London, with interviews designed to touch on perceptions about the potential and realized community-level impact of the RIOTT clinic. Follow-up interviews with key informants found little evidence that community members attributed any changes in community-level outcomes to RIOTT implementation. This qualitative evidence was consistent with pre-post comparisons of official crime statistics from Camberwell Green Ward (the location of the RIOTT program) showing no significant differences in per capita crime rates following RIOTT's implementation. Since only 35 individuals were enrolled in the RIOTT program over the study period, it is unsurprising that both qualitative and quantitative evidence from this article showed no effect. However, a complementary study conducted by the same research team found suggestive evidence that participation in RIOTT had beneficial effects of reduced anti-social behavior for a small number of HAT participants previously identified on the Camberwell Street Population Forum (Miller et al., 2011).

Finally, van den Brink and Blanken (2002) described incidents related to public order and public safety that occurred in the treatment center or in its surrounding environments during the Dutch trials. While results were presented separately for the injectable and inhalable heroin treatment arms, outcomes were similar and thus are combined in our discussion. Throughout the

12-month duration of the heroin trials, there were a total of 191 events involving 109 (34.9%) of the 312 patients in the heroin treatment arms. Of all 191 incidents involving study participants, 50 (26.2%) involved smuggling or attempting to divert heroin medication out of the study site; 38 (19.9%) involved illicit drug use and/or distribution; 26 (13.6%) involved physical aggression; 45 (23.6%) involved verbal aggression; and the remainder concerned house rule violations. Only 28 of these 191 events (14.7%) occurred outside the center, and these most commonly involved public order disturbance, vagrancy, public consumption of illicit drugs, and illicit drug dealing. An additional 20 events involving similar complaints were reported by neighborhood residents as occurring in proximity to the treatment centers but could not be directly attributed to a particular patient. While this evidence indicates that patients involved in HAT trials may generate some incidents that affect the community, there is no information to allow comparison with patients in the methadone treatment arm – nor is it possible to estimate the counterfactual of the extent to which public disorder or safety would have been affected had these individuals not participated in the trial.

Summary of Findings for Community-Level Outcomes

Our review of the literature found no adverse effects of HAT on community-level outcomes of public disorder and crime and some positive effects. There are, however, three significant limitations concerning this conclusion. First, the relevant literature is very small and included no RCTs and no quasi-experimental studies with a comparison group. Second, the trials for which community-level outcomes were studied enrolled relatively few participants, making it hard to detect adverse (or beneficial) effects at the community level; it is unclear the extent to which this evidence base would generalize to larger scale implementation of HAT. Third, the outcome measures studied to date do not address many of the community-level concerns raised about HAT (e.g., normalization of heroin use, traffic accidents, and diversion of pharmaceutical heroin to illicit markets).

The processes by which HAT clinics operate may also determine their effects on the broader community. For instance, the RIOTT program site in South London operated out of an existing community-based alcohol and other drug use service provider's clinic, a facility which already provided oral methadone or other services to about 300 patients. By incorporating HAT into existing facilities, there may have been less realized and/or perceived impact on the community in which the clinic was located. Operating hours, capacity, accessibility, and the availability of other social services within HAT facilities are also likely to be important factors in determining community impact. Furthermore, it likely that HAT implementation could generate heterogenous community-level impacts depending on where clinics are located. To date, all HAT facilities have been located in urban areas. Proximity to other service providers, the existence and characteristics of local drug markets, and the pre-existing socioeconomic and built environment

characteristics of the communities where HAT facilities are located may interact to generate differential impact for both patient-level outcomes as well as community-level outcomes.

Finally, by exploiting the timing of heroin-assisted RCTs' implementation to measure community-level impact, the evidence base has implicitly embedded the procedures taken by each RCT, some of which were designed specifically to limit community impact. For instance, all RCTs have imposed some type of residency requirement (see **Appendix Table A2**), limiting the extent to which opioid dependent individuals might migrate to the trial cities to receive HAT. Additionally, several trials have discharged HAT participants for violating program rules by attempting to divert medications outside the treatment facility, suggesting that efforts to prevent attempted diversion may be important for wider HAT implementation. Overall, the ability to generalize existing evidence to allowing HAT outside an RCT context will depend on the specific design, implementation, and enforcement of allowing broader HAT availability.

6. Results for Effects of Heroin-Assisted Treatment on Economic Outcomes

We identified three systematic reviews evaluating evidence for the economic effectiveness of different opioid use disorder interventions (Chetty et al., 2017; Murphy and Polsky, 2016; Simoens et al., 2006), two of which focused on pharmacological maintenance therapies (Chetty et al., 2017; Simoens et al., 2006). The four HAT source studies discussed in these reviews were all captured by our search strategy. Our search yielded two additional studies evaluating the costs or cost-benefits of HAT (Frei, 2001; van den Brink and Blanken, 2002), and we became aware of one recent relevant cost-effectiveness study published outside our search timeframe (Bansback et al., 2018).

These seven articles spanned five RCTs and one Swiss prospective cohort study. In addition, one article used estimates from the Swiss study to model potential economic impacts of HAT provision in the Canadian context. Below, we provide a narrative review of the findings from these seven articles, organized by study. We also point the interested reader to the excellent review by Strang et al. (2012), which provides a detailed discussion of costs and implementation of supervised injectable heroin studies conducted in Europe.

Swiss PROVE study. Frei (2001) conducted a cost-benefit analysis of the Swiss HAT program based on data collected as part of the PROVE cohort study in 1994. Program costs -- included the direct costs of prescribed heroin provision, labor, and other operating costs (e.g., heightened security costs) – were estimated at 18,677 Swiss francs (CHF) per patient per year. Benefits included costs savings from lower costs of accommodations, increased productivity, societal savings from reduced criminal activity, and medical expenditure savings from health improvements. Benefits attributable to HAT were estimated by comparing patient outcomes pre-post enrollment in HAT, and both costs and benefits were monetized on a per patient per day basis. Findings showed a net benefit of HAT of 44 CHF per person-day, driven largely by criminal justice savings.

However, these estimates were based on a single-group pre-post study design that compared baseline characteristics for a cohort of HAT patients who were retained in treatment for at least 18 months (69% treatment retention rate). It is important to note that this approach makes the very strong assumption that all changes in behavior observed over the course of HAT were in fact caused by HAT, not by regression to the mean, maturation, or other factors that may have impacted both treatment retention and improved outcomes for the study population. Additionally, the study design did not allow for calculation of the cost-benefits of other alternative treatment options for a comparable population.

Parameter estimates from the Swiss study were used by Miller et al. (2004) to model the potential economic impact of implementing a supervised injectable heroin program in Greater

Vancouver, Canada. Combining results from the Swiss study on changes in hospitalization, emergency room utilization, criminal activity, and employment with cost estimates from the Vancouver Injection Drug Users Study, the authors' simulation models showed potential five-year cost savings from implementing a HAT program in Vancouver of approximately C$9,650 per person treated.

Dutch Trials. Two studies evaluated economic outcomes associated with HAT provision based on the two Dutch trials (Dijkgraaf et al., 2005; van den Brink and Blanken, 2002). van den Brink and Blanken (2002) described costs for implementing the HAT trials across different levels of implementation. Their results showed estimated annual costs per patient per treatment year of approximately €27,000, €20,000, and €15,000 for treatment centers that serviced 25, 50, or 75 patients respectively. Across all scenarios, personnel accounted for over two-thirds of costs (70-75%), with about half of personnel costs due to the requirement of at least two full-time nurses on-site during operating hours.

Dijkgraaf et al. (2005) conducted a cost-utility analysis comparing co-prescribed heroin to oral methadone based on evidence pooled across the inhalable and injectable heroin-assisted treatment Dutch trials. Their intent-to-treat (ITT) analysis adopted a societal perspective covering the 12-month trial period. Consequences were measured by quality adjusted life years (QALYs) using a standardized instrument (Euroqol EQ-5D), and costs or cost savings included those associated with program costs (e.g., medication, staff, overhead), healthcare utilization (e.g., consultations, institutional inpatient stays), program-related travel, and criminal justice costs (e.g., law enforcement investigations, prosecution, incarceration, and damage to victims). Of note, criminal justice costs only included property and violent crimes, without consideration of costs related to illicit drug possession or distribution. Furthermore, because the original trial evidence could not be used to estimate potential damage to victims of crime, the authors relied on unpublished estimates of crime victim counts based on a sub-study of 51 HAT participants.

Unit costs were drawn from program materials or the literature and were indexed to the year 2001. Differential costs and cost savings were calculated by comparing average differences across ITT groups during the duration of the 12-month trial period; the implicit assumption is that the randomization process resulted in balanced baseline characteristics across groups.

Findings showed that average per-patient program costs for heroin co-prescription (€17,634 per patient) significantly exceeded those for oral methadone (€1,412 per patient), with differential average costs per patient in 2001 prices of €16,222 (lower limit €15,084; $p<0.0001$). However, higher program costs were more than offset by criminal justice cost savings, driven primarily by lower estimated costs from damage to victims of crime, resulting in an estimated total net savings from HAT of €12,793 (95% CI = €1,083, €25,229) per patient per year. In addition, relative to oral methadone, co-prescription of heroin was associated with 0.058 more QALYs per patient per year (95% CI = 0.016, 0.099). Overall findings were more strongly in favor of HAT if program costs excluded the costs of rebuilding the existing treatment centers used for heroin provision in the trials.

Canadian NAOMI Trial. Nosyk et al. (2012) combined data from the Canadian NAOMI trial with external data sources to conduct a semi-Markov cohort model comparing the incremental cost-effectiveness of supervised injectable heroin relative to oral methadone over several different time horizons, ranging from 1 year to total lifetime. Their primary model adopted a societal perspective and was designed to account for the recurrent nature of opioid dependence, whereby individuals transitioned between treatment (heroin-assisted patients could transition to methadone), relapse, abstinence, and death. Costs in 2009 Canadian dollars (C$) included treatment costs of prescribed heroin and/or methadone derived from NAOMI, costs of treatment for HIV or hepatitis C virus infection, other healthcare costs, criminal justice costs, and costs of damages to victims of crime. Health utility was operationalized as QALYs using a standardized instrument (EQ-5D).

Model results showed that, relative to oral methadone, HAT resulted in higher QALYs and greater cost savings across all time horizons studied. Over a lifetime horizon, the heroin-assisted group accumulated 0.46 more discounted QALYs (a gain of 7.92 QALY [95% CI of 7.32 – 8.53] vs. 7.46 for methadone [95% CI of 6.91 – 8.01). They also generated very slightly lower social costs relative to the methadone group (a point estimate of C$1.10 million with a 95% CI of 0.72 – 1.71 million vs. methadone costs of C$1.14 million, with 95% CI of 0.74 – 1.78 million). Findings were robust across most sensitivity analyses, although in analysis adopting a narrower perspective of the Ministry of Health (and hence excluding criminal justice and victim damage costs) HAT remained cost-effective but no longer yielded cost-savings. Additionally, if one considers the 1-year time horizon over which the NAOMI trial was actually conducted, the health utility of HAT relative to methadone is reduced to 0.01 QALYs and the cost differential is also greatly reduced (C$85,900 vs. C$87,700).

As in the Dutch cost-effectiveness analysis, treatment costs of HAT greatly exceeded those of methadone treatment (monthly costs of C$1,415 vs C$329), and cost savings were largely attributable to reduced criminal justice costs. Estimates for criminal activity were based on self-reported data from NAOMI participants, supplemented with follow-up data from courthouse records up to two years following trial discontinuation and adjusted for baseline offense rates. Only costs from property and violent crimes were considered, and costs of incarceration were excluded. Furthermore, unlike in the Dutch RCT economic analysis, the differential criminal justice costs accrued by those in HAT relative to methadone treatment in Nosyk et al. (2012) are not driven by differences in rates of criminal activity while undergoing treatment. Evidence collected during the NAOMI trial showed similar rates of criminal activity for the HAT and methadone groups while engaged in treatment as well as while in the relapse state (although the likelihood of engaging in criminal activity while in the relapse state was significantly higher). Since their semi-Markov model assumed, based on data collected outside the NAOMI trial, that the probability of transitioning from HAT to relapse was far lower than the probability of transitioning from methadone to relapse (37.0% vs. 95.9%), criminal justice costs are significantly lower in the HAT group. Additionally, the model assumes that patients in HAT

transition to abstinence at a higher rate than patients in methadone do (22.4% for HAT vs. 4.1% for methadone); an assumption based on estimates derived outside the NAOMI trial.

UK RIOTT Trial. One study evaluated the cost-effectiveness of supervised injectable heroin, supervised injectable methadone, and oral methadone treatment based on results from the UK RIOTT trial (Byford et al., 2013). Their analyses, which covered the 6-month trial period, considered both a societal perspective and the perspective of the UK National Health Service (which excluded crime and criminal justice costs). For the societal perspective, costs included program costs of the medication, clinic operations and staffing, case management and urine tests; costs of other service utilization (e.g., accommodation, healthcare utilization, social services); incarceration costs; and costs of crimes committed over the 26-week trial period. Effectiveness was operationalized as QALYs based on the EQ-5D, and costs were calculated as 2007/08 pounds (£).

Findings showed programmatic costs per participant for heroin (£8,995) significantly exceeded those for both injectable methadone (£4,674) and oral methadone (£2,596). However, once total service utilization and crime costs were incorporated, oral methadone was the costliest treatment method (£15,805), followed by injectable heroin (£13,410) and injectable methadone (£10,945). As with the previously discussed studies, this was largely driven by higher crime rates among the oral methadone group. Since QALYs were only slightly higher among injectable heroin group (0.27 vs 0.24 in both methadone groups), injectable methadone showed the highest probability of being cost-effective based on the UK National Institute for Health and Care Excellence (NICE) cost-effectiveness threshold of £30,000 per QALY gained.

Of note, while clinic and staffing costs drove some of the higher programmatic costs of supervised injectable heroin treatment provision, higher drug costs were also a significant factor. The average drug costs per participant for the supervised injectable heroin arm were £1,814 over the 26-week trial period, while they were only £720 and £205 for the injectable and oral methadone arms, respectively. Based on threshold analysis, Byford et al. (2013) estimated the price of pharmaceutical injectable heroin would have to fall from £12.50 per 500mg preparation (the price paid by the RIOTT clinics) to £2 per 500mg preparation for injectable heroin to have a higher probability of cost-effectiveness than injectable methadone.

Canadian SALOME Trial. Bansback et al. (2018) compared the cost-effectiveness of supervised injectable heroin and supervised injectable hydromorphone based on findings from the SALOME trial. Their analyses adopted a societal perspective and considered a within-trial timeframe of 6 months as well as a lifetime timeframe. For the latter, they extended the semi-Markov model developed previously (Nosyk et al., 2012), and incorporated data from the NAOMI trial to compare cost-effectiveness of the injectable treatments with oral methadone. Costs included programmatic costs (e.g., medication, staffing, and overhead), costs of drug treatment for HIV infection, other healthcare service utilization, and criminal justice and crime costs (including victim damages). Effectiveness was operationalized as QALYs based on the EQ-5D, and costs were adjusted to 2015 dollars.

Based on the within-trial analysis adjusted for baseline differences across treatment groups, injectable hydromorphone provided slightly higher additional QALYs relative to injectable heroin (0.002, 95% CI = -0.018, 0.023), but also higher social costs ($15,510, 95% CI = -$9,955, $43,706) due largely to higher costs of involvement in crime. However, this estimate came from unadjusted analyses of crime differences and was imprecisely estimated; the confidence intervals for costs of crime overlapped across treatment modalities. Given neither incremental benefits nor costs significantly differed between the two treatments, the estimated probability that hydromorphone was more cost-effective than heroin was only 16%. Similarities between injectable hydromorphone and injectable heroin persisted in the model-based estimates over a lifetime horizon, and both were shown to dominate oral methadone in cost-effectiveness. Findings were largely unchanged across sensitivity analyses. While the model-based estimates adjusted for baseline outcomes across treatment arms, differential costs between treatment modalities are largely driven by parameter assumptions regarding state transition probabilities.

Summary of Findings for Economic Outcomes

Overall, evidence across studies finds that supervised injectable HAT is much more expensive than oral methadone but is more cost-effective in a societal sense, primarily because the models credit HAT with doing more to reduce participants' levels of criminal justice involvement and associated damages to victims of their crime activity. Most trials also showed higher QALYs among the HAT arm. Among the two studies comparing the cost-effectiveness of supervised injectable heroin to other supervised injectable medications (injectable methadone or injectable hydromorphone), there were no significant differences between injectable heroin or the other injectables in terms of costs or QALYs. While further evidence is needed, combined with evidence of hydromorphone noninferiority from the SALOME trials, this suggests that supervised injectable hydromorphone may offer a preferable alternative to HAT in regimes that can support the higher programmatic costs of injectable treatments but that face particular political, legal, or regulatory barriers to allowing treatment with pharmaceutical heroin.

There are several limitations to these findings, including the fact that some outcomes of interest are difficult to monetize. First, the estimates for crime costs in several cases either do not adjust for baseline crime rates or are dependent on model assumptions drawn from evidence outside the trial data. Second, several costs are omitted from analyses. Only one study (Dijkgraaf et al., 2005) incorporated the costs to participants of program-related travel. None of the RCT studies incorporated potential gains in productivity, which may be important to consider over longer time horizons. Crime costs seem to have been restricted to property and violent crimes, excluding costs associated with illicit drug dealing, prostitution/solicitation, disorderly conduct, or major traffic violations. Third, while several studies incorporated some of the costs of and QALY losses associated with HCV and HIV among the patient population, the potential economic implications of reduced transmission of HIV and HCV to the broader population due

to reduced injection of illicit heroin were not explicitly modelled. Also, to our knowledge, no economic analysis considered potential benefits from reduced chronic skin and soft tissue infections, which significantly contribute to morbidity and premature mortality among people who inject drugs (Harris et al., 2018; Larney et al., 2017). Finally, when considering economic outcomes for wider scale implementation of HAT, one might also evaluate the potential effects of HAT on costs within the methadone treatment system; however, we did not identify any empirical evidence to this effect.

Additionally, all reviewed studies found significantly higher costs of providing heroin-assisted treatment relative to oral methadone, and these higher total costs may serve as an important barrier to implementation, regardless of findings on cost-effectiveness. The high costs of renovating existing facilities to meet the requirements for a heroin-assisted treatment center in Vancouver were noted as a primary factor for the nearly two-year delay in identifying a Vancouver site for the NAOMI trial (Gartry et al., 2009). When considering implementation of HAT outside of a clinical trial setting, one must also consider who will be responsible for the costs of treatment provision. Requiring patients to pay out-of-pocket would likely severely limit participant uptake; requirements for insurance to cover HAT costs would need to be negotiated and may prove intractable; and the likely governmental funders of HAT, health and healthcare agencies, are not the agencies where the bulk of savings are accrued.

7. Summary of Findings

Based on evidence from ten RCTs, our review found that, for individuals with chronic heroin use disorder who have not responded to conventional medication treatments, HAT co-prescribed with flexible doses of oral methadone offers significant benefits over oral methadone with respect to improving treatment retention, although there are several nuances in interpreting these results with respect to both the HAT trials in particular as well as to the treatment of opioid use disorder more broadly (see Vogel et al. (2017) for discussion). For individuals with chronic treatment-refractory heroin use disorder, co-prescribed HAT also seems to offer significant benefits relative to oral methadone alone in terms of reducing illicit heroin use and criminal activity. More limited evidence shows that co-prescribed HAT may have some benefits over oral methadone alone for improving physical health and mental health; and the treatments do not seem to significantly differ with respect to influencing other substance use, social functioning, and mortality. RCTs have also consistently shown a higher risk of medication-related serious adverse events for individuals receiving HAT relative to individuals receiving oral methadone; however, at least within the trial context, the higher risk of serious adverse events does not translate to higher risk of mortality.

These findings are based on a review of the results of ten RCTs that have been implemented across seven countries. While the RCTs have varied somewhat in how both the experimental and control conditions have been implemented, our summary findings are largely reflective of comparisons between supervised injectable heroin treatment (plus optional oral methadone) and oral methadone treatment. Importantly, given participant eligibility requirements, the evidence base reviewed should also largely be interpreted as one that informs the comparative effectiveness of HAT for treatment of heroin use disorder among a patient population that has previously attempted but not responded to oral methadone treatment. Findings are thus not intended to provide evidence regarding the use of HAT as a first-line treatment option. These conclusions also may not generalize to comparisons of supervised injectable heroin with other medication treatments (e.g., buprenorphine); or to the effectiveness of HAT delivered through other routes of administration (e.g., oral heroin). Furthermore, the supervised nature of HAT delivery mandated in nearly all identified RCTs means we cannot disentangle to what extent the relative benefits from HAT are accrued because of the medication itself or because of the structured routine that coming to the facility to receive study medication entails. In addition, while the experimental design of the reviewed studies bolsters a causal interpretation of the findings, the reliance on RCT evidence also potentially limits the generalizability of our conclusions. Still the evidence for the effectiveness of HAT relative to oral methadone treatment is markedly consistent across RCTs regarding the primary outcomes of treatment retention and illicit heroin use.

Our review of community-level and economic outcomes identified a much smaller set of studies. We identified five descriptive or quasi-experimental studies that evaluated the potential community-level impacts of HAT. Overall, these studies do not suggest large impacts of HAT implementation on the broader community, although the empirical strategies used in prior research largely rely on community-level changes induced by HAT RCT implementation as opposed to wider integration of HAT into the standard healthcare system as has been done in Switzerland and Denmark. Additionally, community-level concerns have a clear impact on the feasibility of implementing HAT. Therefore, it would be beneficial for future research to employ causal inference methods to evaluate the impact of HAT in countries where it has been implemented and for future trials to consider embedding evaluation of community-level outcomes within their research design.

Finally, the literature shows that the programmatic costs of supervised injectable treatments greatly exceed the programmatic costs of oral methadone treatment, but that the higher programmatic costs are more than offset by greater cost savings from crime damages and criminal justice involvement. However, the costs associated with damages to victims of crime perpetrated by study participants were generally calculated using estimates of the average cost of certain crime types that were derived outside of the study context. The validity of these estimates thus hinges on a number of assumptions, which merit further consideration within the context of these trials. Additionally, further research evaluating how the costs and cost-effectiveness of HAT may vary as a function of scale or the setting in which it is implemented could help shed more light on economic outcomes associated with HAT implementation outside the trial context.

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Appendix A. Details on Heroin-Assisted Treatment Randomized Controlled Trials

As of June 2018, ten RCTs have compared the effectiveness of heroin-assisted treatment to alternative treatments for opioid use disorder. These trials, conducted over nearly four decades, span seven countries. Table A.1 describes the experimental and control conditions, sample size, and treatment duration across the ten RCTs. Table A.2 documents the eligibility requirements for participation in the RCTs. Table A.3 provides references for study protocols or information on recruitment and study participants, and Table A.4 briefly describes any additional services offer to trial participants. Table A.5 notes how studies measured substance use and criminal activities.

Table A.1. Overview of Heroin-Assisted Treatment Randomized Controlled Trials

Trial	Setting (timeframe)	Treatment (T)	Control (C)
Early UK	Single clinic in London (1972–1975)	Unsupervised injectable heroin	Oral methadone treatment (MT)
Swiss trial	Single clinic in Geneva, Switzerland (1995–1996)	Supervised injectable heroin (SIH) plus optional oral MT	Any other conventional drug treatment
Dutch injectable trial	8 treatment units in 6 cities in Netherlands (1998–01)	SIH + optional oral MT	Oral MT
Dutch inhalable trial	8 treatment units in 6 cities in Netherlands (1998–01)	**T1**: SIH + optional oral MT **T2**: Oral MT for 6mo then inhalable heroin + optional oral MT for 6mo	Oral MT
Spain PEPSA	1 hospital in Granada, Spain (2001–2004)	SIH + oral MT	Oral MT
German study	Seven cities in Germany (2002–2004)	SIH + optional oral MT plus: **T1**: psychoeducation, counseling **T2**: case management, motivational interviewing	Oral T plus: **C1**: education **C2**: case management
Canada NAOMI	3 cities in Canada (2005-2008)	**T1**: SIH + optional oral MT **T2**: Supervised injectable hydro-morphone + optional oral MT	Oral MT
UK RIOTT	Three sites in England (2005-2008)	**T1**: SIH + optional oral MT **T2**: Supervised injectable MT + optional oral MT	Optimized oral MT
TADAM	Liège, Belgium (2011-2013)	Supervised injectable or inhalable heroin + optional oral MT	Oral MT
SALOME	Vancouver, Canada (2011-2013)	SIH + optional oral MT	Supervised injectable hydromorphone + optional oral MT

Table A.2. Details of Participant Eligibility and Exclusion Conditions in Heroin-Assisted Treatment Randomized Controlled Trials

Trial (Setting)	Eligibility	
Early UK RCT (London)	Use or use disorder:	▪ Heroin dependent (level of severity based on staff judgment); daily injection of heroin for at least 3 months
	Prior treatment:	▪ Persistently asks for HAT & rejects alternative treatments
	Other:	▪ Age 18-35; eligible for National Health Service treatment; residing in greater London area
	Exclusions	▪ Psychotic
Swiss RCT (Geneva)	Use or use disorder:	▪ Intravenous (IV) heroin dependence 2+ years (based on ICD); daily opiate use
	Prior treatment:	▪ Two or more previous attempts at treatment
	Other:	▪ Aged 20+; Geneva resident since June 1994; willing to give up driving once started HAT; social distress and/or poor health due to drug use
	Exclusions:	▪ None noted
Two Dutch RCTs (Netherlands)	Use or use disorder:	▪ Heroin dependence for 5+ years (based on DSM); (near) daily illicit heroin use
	Prior treatment:	▪ Regularly attended methadone treatment during previous 6 months; used 50mg or 60mg methadone or more daily for uninterrupted >=4 weeks in previous 5 years
	Other:	▪ Aged 25+; poor health or social functioning; local resident at least 3 years
	Exclusions	▪ Severe health problems; history of aggressive behavior; more severe non-opiate dependence; pregnant or breastfeeding; had not voluntarily ceased heroin use for more than 2 months in previous year; require MT>150mg per day; life expectancy <12 months
PEPSA RCT (Spain)	Use or use disorder	▪ Opiate dependency for 2+ years (based on ICD); ongoing IV opioid habit
	Prior treatment	▪ Been in medication treatment in the past at least twice
	Other	▪ Age >18 years; resident in Granada over the preceding year; currently presenting 2+ of: mental health problems, infectious disease related to IV drug use, or social maladjustment
	Exclusions	▪ Imminent imprisonment (or similar legal/social barrier); any disability that might prevent the participants from attending the center autonomously; pregnancy
German multisite RCT (Germany)	Use or use disorder:	▪ Diagnosis of opioid dependence for at least 5-year duration (ICD)
	Prior treatment:	▪ Participation in previous drug treatment OR ongoing MT for 6+ months with continued IV use of street heroin
	Other:	▪ Age 23+; poor physical and/or mental health; local resident at least 5 years
	Exclusions	▪ Pending jail sentence; severe physical disorder; abstinent for at least 2 of past 12 months
NAOMI RCT (Canada)	Use or use disorder:	▪ Current opioid dependence (DSM); opioid use for 5+ years with daily opioid injection
	Prior treatment:	▪ 2+ prior treatments, at least one for MT; not enrolled in MT for prior 6 months
	Other:	▪ Age 25+; no change in city residence for at least 1 year

	Exclusions	▪ Severe medical or psychiatric conditions that contraindicated HAT; pregnancy; criminal justice issues that could have resulted in extended incarceration over trial period
RIOTT multisite RCT (UK)	Use or use disorder	▪ 3+ year history of injecting heroin use
	Prior Treatment	▪ Inject illicit heroin at least 50% days in preceding three months despite receiving continuous conventional oral MT for at least 6 months
	Other	▪ Age 18-65 at recruitment; resident of London, Brighton, or Darlington
	Exclusions	▪ Significant active medical/psychiatric condition; alcohol dependent; regular abuse of benzodiazepines; pregnant or breastfeeding; impending prison sentence
TADAM RCT (Belgium)	Use or use disorder	▪ Heroin dependent 5+ years; (almost) daily use of street heroin; injected or inhaled heroin administration
	Prior treatment	▪ At least one previous experience of MT (with minimum daily dosage 60mg)
	Other	▪ Age 20+; legal residents in Liège for at least 1 year; poor health or criminal involvement
	Exclusions	▪ None noted
SALOME (Canada)	Use or use disorder	▪ Opioid dependence 5+ years (DSM); regular injection of street opioids in past year; current injection of street opioids
	Prior treatment	▪ 2+ prior addiction treatment episodes, with at least one for medication treatment
	Other	▪ Age 19+; residing in greater Vancouver area
	Exclusions	▪ Severe medical conditions contraindicated; pregnant or planning to become pregnant

Table A.3. Sources for Additional Information on HAT Randomized Controlled Trials

Trial (Setting)	Source for trial protocols
Early UK RCT (London)	Hartnoll et al. (1980)
Swiss RCT (Geneva)	Perneger et al. (1998)
Two Dutch RCTs (Netherlands)	Van Den Brink et al. (1999)
PEPSA RCT (Spain)	March et al. (2004)
German multisite RCT (Germany)	Haasen et al. (2007)
NAOMI multisite RCT (Canada)	Oviedo-Joekes et al. (2008)
RIOTT multisite RCT (UK)	Lintzeris et al. (2006)
TADAM RCT (Belgium)	Demaret et al. (2015)
SALOME (Canada)	Oviedo-Joekes et al. (2016)

Table A.4. Details of Treatment Conditions in Heroin-Assisted Treatment Randomized Controlled Trials

Trial	Additional Services
Early UK	Counseling by clinic psychiatrists; hospital admission and referral to a therapeutic community available as normal
Swiss trial	All HAT participants were offered HIV prevention, social & legal support, primary care, and psychological counseling; control group participants were not precluded from receiving additional services but were not offered such services explicitly through the program
Two Dutch trials	Offered psychosocial services, including individual counseling, group counseling, housing and budget assistance, participation in work projects and standard medical and psychiatric treatment
Spain PEPSA	All received clinical, social, legal support, and psychological services
German study	Psychosocial care with (attempted) weekly contacts mandatory
Canada NAOMI	All patients offered a comprehensive range of primary care and psycho-social services
UK RIOTT	All assigned a case worker, medical reviews, and access to psychological services. Other health or social services available.
TADAM	All offered psychosocial services
SALOME	Access to a pre-specified range of primary care services and a psychosocial support worker who offered individual counselling and case management services.

Table A.5. Measurement Methods for Illicit Drug Use and Criminal Activities in Heroin-Assisted Treatment Trials

Experimental v Control		
Study: Follow-up	**Illicit drug use measure**	**Measurement**
Unsupervised injectable heroin v oral methadone		
Early UK trial: 12 months	Daily average illicit opiate use over past 12 months	Self-report; Urinalysis
	Non-opiate illicit substance use	Self-report; Urinalysis
	Crime as source of income over past year	Self-report
	Number of arrests over past year	Official record
	Incarceration/imprisonment	Official record
Supervised injectable heroin (+ oral methadone) v other drug treatment		
Swiss trial: 6 months	Daily use of street heroin	Self-report (ASI)
	Daily use alcohol, tobacco, or other drugs	Self-report (ASI)
	Charged in past 6 months	Self-report
	Commercial sex in past 6 months	Self-report
Supervised injectable heroin (+ oral methadone) v oral methadone		
Dutch trial: 12 months	Average days illicit heroin use during past month	Self-report; urinalysis
	Average days illicit activities during past month	Self-report
Spain PEPSA: 9 months	Days street heroin use in past month	Self-report (ASI)
	Days per month involved in illegal activities	Self-report (ASI)
German trial: 12 months	>50% negative specimens for street heroin and no increase in cocaine use in the past month	Urine/hair analysis; self-report
	Criminal activity	Self-report (ASI); official records
NAOMI: 12 months	Use of street heroin at least one day of past month	Self-report (ASI)
	Days use of illicit drugs in past month	Self-report (ASI)
	Illegal activities	Self-report (ASI)
UK RIOTT: 6 months	>50% negative specimens for street heroin, past 12 weeks	Urinalysis
	Criminal offenses	Self-report (ASI)
Supervised injectable heroin or methadone (+ oral methadone) v oral methadone		
UK RIOTT: 6 months	>50% negative specimens for street heroin, past 12 weeks	Urinalysis
	Criminal offenses	Self-report (ASI)
Supervised injectable or inhalable heroin (+ oral methadone) v oral methadone		
Belgium TADAM: 12 months	Days illicit heroin use in past month	Self-report (ASI); urinalysis
	Days cocaine use in past month	Self-report (ASI); urinalysis
	Days benzodiazepine use in past month	Self-report (ASI)
	# acts committed or experienced as victim, past-month	Self-report; official record
Supervised inhalable heroin (+ oral methadone) v oral methadone		
Dutch trial: 12	Average days illicit heroin use during past month	Self-report; urinalysis

months	Average days illicit activities during past month	Self-report

Appendix B. Details on Search Strategy and Excluded Results

Details on Search Strategy

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 1/1/1990-1/17/2018

LANGUAGE:
ALL

SEARCH STRATEGY
"heroin assisted" OR heroin-assisted OR heroin prescri* OR "heroin maintenance" OR prescri* heroin OR "pharmaceutical heroin" OR "hydromorphone assisted" OR "hydromorphone-assisted" OR "hydromorphone maintenance" OR "diacetylmorphine assisted" OR diacetylmorphine-assisted OR diacetylmorphine prescri* OR prescri* diacetylmorphine OR "diacetylmorphine maintenance" OR "diamorphine assisted" OR diamorphine-assisted OR diamorphine prescri* OR prescri* diamorphine OR "diamorphine maintenance"
AND
therapy OR therapeutic* OR treatment OR treated OR treating
AND
dependence OR disorder OR addict* OR abuse OR abuser* OR "Substance-Related Disorders"[Mesh] OR harm reduc*

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DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 1/1/1990-1/17/2018

LANGUAGE:
ALL

SEARCH STRATEGY
“Similar Article” searches on the following 2 articles:

Ferri, Marica, Marina Davoli, and Carlo A. Perucci. "Heroin maintenance for chronic heroin-dependent individuals." Cochrane Database Syst Rev 8 (2010).

Nosyk, Bohdan, Daphne P. Guh, Nicholas J. Bansback, Eugenia Oviedo-Joekes, Suzanne Brissette, David C. Marsh, Evan Meikleham, Martin T. Schechter, and Aslam H. Anis. "Cost-effectiveness of diacetylmorphine versus methadone for chronic opioid dependence refractory to treatment." Canadian Medical Association Journal 184, no. 6 (2012): E317-E328.

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DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science – 1/1/1990-1/17/2018

LANGUAGE:
ALL

SEARCH STRATEGY
"Forward" searches on the following 2 articles:

Ferri, Marica, Marina Davoli, and Carlo A. Perucci. "Heroin maintenance for chronic heroin-dependent individuals." Cochrane Database Syst Rev 8 (2010).

Nosyk, Bohdan, Daphne P. Guh, Nicholas J. Bansback, Eugenia Oviedo-Joekes, Suzanne Brissette, David C. Marsh, Evan Meikleham, Martin T. Schechter, and Aslam H. Anis. "Cost-effectiveness of diacetylmorphine versus methadone for chronic opioid dependence refractory to treatment." Canadian Medical Association Journal 184, no. 6 (2012): E317-E328.

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DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science – 1/1/1990-1/17/2018

LANGUAGE:
ALL

SEARCH STRATEGY
ts=((heroin NEAR/2 assisted) OR 'heroin-assisted' OR (heroin NEAR/2 prescri*) OR (heroin NEAR/2 maintenance) OR 'pharmaceutical heroin' OR (hydromorphone NEAR/2 assisted) OR 'hydromorphone-assisted' OR (hydromorphone NEAR/2 maintenance) OR (diamorphine NEAR/2 assisted) OR 'diamorphine-assisted' OR (diamorphine NEAR/2 prescri*) OR (diamorphine NEAR/2 maintenance) OR (diacetylmorphine NEAR/2 assisted) OR 'diacetylmorphine-assisted' OR (diacetylmorphine NEAR/2 prescri*) OR (diacetylmorphine NEAR/2 maintenance)
AND
ts=(therapy OR therapeutic* OR treatment OR treated OR treating)
AND
ts=(dependence OR dependent OR disorder OR addict* OR abuse OR abuser OR (harm NEAR/2 reduc*))

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DATABASE SEARCHED & TIME PERIOD COVERED:
Scopus – 1/1/1990-1/17/2018

LANGUAGE:
ALL

SEARCH STRATEGY
"Forward" searches on the following 2 articles:

Ferri, Marica, Marina Davoli, and Carlo A. Perucci. "Heroin maintenance for chronic heroin-dependent individuals." Cochrane Database Syst Rev 8 (2010).

Nosyk, Bohdan, Daphne P. Guh, Nicholas J. Bansback, Eugenia Oviedo-Joekes, Suzanne Brissette, David C. Marsh, Evan Meikleham, Martin T. Schechter, and Aslam H. Anis. "Cost-effectiveness of diacetylmorphine versus methadone for chronic opioid dependence refractory to treatment." Canadian Medical Association Journal 184, no. 6 (2012): E317-E328.

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DATABASE SEARCHED & TIME PERIOD COVERED:
Scopus – 1/1/1990-1/17/2018

LANGUAGE:
ALL

SEARCH STRATEGY
TITLE-ABS-KEY (heroin W/2 assisted) OR 'heroin-assisted' OR (heroin W/2 prescri*) OR (heroin W/2 maintenance) OR (pharmaceutical W/2 heroin) OR (hydromorphone W/2 assisted) OR 'hydromorphone-assisted' OR (hydromorphone W/2 maintenance) OR (diamorphine W/2 assisted) OR 'diamorphine-assisted' OR (diamorphine W/2 prescri*) OR (diamorphine W/2 maintenance) OR (diacetylmorphine W/2 assisted) OR 'diacetylmorphine-assisted' OR (diacetylmorphine W/2 prescri*) OR (diacetylmorphine W/2 maintenance)
AND
therapy OR therapeutic* OR treatment OR treated OR treating
AND
dependence OR dependent OR disorder OR addict* OR abuse OR abuser OR (harm W/2 reduc*)
AND
EXCLUDE (EXACTKEYWORD , "Nonhuman ")

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DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 1/1/1990-1/17/2018

LANGUAGE:
ALL

SEARCH STRATEGY
(heroin NEAR/2 assisted) OR 'heroin-assisted' OR (heroin NEAR/2 prescri*) OR (heroin NEAR/2 maintenance) OR 'pharmaceutical heroin' OR (hydromorphone NEAR/2 assisted) OR 'hydromorphone-assisted' OR (hydromorphone NEAR/2 maintenance) OR (diamorphine NEAR/2 assisted) OR 'diamorphine-assisted' OR (diamorphine NEAR/2 prescri*) OR (diamorphine NEAR/2 maintenance) OR (diacetylmorphine NEAR/2 assisted) OR 'diacetylmorphine-assisted' OR (diacetylmorphine NEAR/2 prescri*) OR (diacetylmorphine NEAR/2 maintenance)
AND
therapy OR therapeutic* OR treatment OR treated OR treating
AND
dependence OR disorder OR addict* OR abuse OR abuser OR (harm NEAR/2 reduc*) OR 'drug dependence treatment'/exp

AND
Human

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DATABASE SEARCHED & TIME PERIOD COVERED:
WorldCat– 1/1/1990-1/17/2018

LANGUAGE:
ALL

SEARCH STRATEGY
kw: prescription w3 heroin

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DATABASE SEARCHED & TIME PERIOD COVERED:
WorldCat– 1/1/1990-1/18/2018

LANGUAGE:
ALL

SEARCH STRATEGY
(kw: heroin n2 assisted) OR kw: 'heroin-assisted' OR (kw: heroin n2 maintenance) OR (kw: pharmaceutical n2 heroin) OR (kw: hydromorphone n2 assisted) OR kw: 'hydromorphone-assisted' OR (kw: hydromorphone n2 maintenance) OR (kw: diamorphine n2 assisted) OR kw: 'diamorphine-assisted' OR (kw: diamorphine n2 prescri*) OR (kw: diamorphine n2 maintenance) OR (kw: diacetylmorphine n2 assisted) OR kw: 'diacetylmorphine-assisted' OR (kw: diacetylmorphine n2 prescri*) OR (kw: diacetylmorphine n2 maintenance)

Excluded Reviews from Full-Text Screen

Table B.1. Superseded systematic reviews

Superseded Systematic Review(s)	Superseding Systematic Review
Ferri et al. (2003); Ferri et al. (2005); Ferri et al. (2006)	Ferri et al. (2011)
Perry et al. (2013)	Perry et al. (2015)
Strang et al. (2012)	Strang et al. (2015)

Table B.2. Excluded reviews with reasons for exclusion

#	Reference	Reasons for exclusion
1	Bammer, Gabriele. *International Perspectives on the Prescription of Heroin to Dependent Users: A collection of papers from the United Kingdom, Switzerland, the Netherlands and Australia*. Canberra: The Australian National University, 1997.	Collection of studies – not a systematic review
2	Brehmer, Cornelia, and Peter X. Iten. "Medical prescription of heroin to chronic heroin addicts in Switzerland—a review." Forensic science international 121, no. 1 (2001): 23-26.	Narrative review of Swiss studies – not a systematic review.
3	Brissette, S. "Medical prescription of heroin--a review." Canadian HIV/AIDS policy & law review 6, no. 1-2 (2001): 1-92.	Not a systematic review
4	Iruín, Álvaro, Íñigo Aizpurua, Joseba Ruiz de Apodaka, Edurne Zapiraín, and Antón Aizpuru. "Revisión de la evidencia científica sobre las alternativas a la metadona en el tratamiento psicofarmacológico de la dependencia a opiáceos." Revista Española de Salud Pública 75, no. 3 (2001): 207-220.	Not a systematic review
5	Zador, Deborah. "Injectable opiate maintenance in the UK: is it good clinical practice?." Addiction 96, no. 4 (2001): 547-553.	Not a systematic review
6	Bell, James, Alain Dru, Benedikt Fischer, Shabtay Levit, and M. Aamer Sarfraz. "Substitution therapy for heroin addiction." Substance use & misuse 37, no. 8-10 (2002): 1149-1178.	Not a systematic review
7	Fischer, Benedikt, Jürgen Rehm, Maritt Kirst, Miguel Casas, Wayne Hall, Michael Krausz, Nicky Metrebian et al. "Heroin-assisted treatment as a response to the public health problem of opiate dependence." The European Journal of Public Health 12, no. 3 (2002): 228-234.	Not a systematic review
8	Gerlach, Ralf. "Drug-substitution treatment in Germany: a critical overview of its history, legislation and current practice." Journal of Drug Issues 32, no. 2 (2002): 503-522.	Not a systematic review; does not include studies on intervention of interest
9	Ladewig, Dieter, Kenneth M. Dürsteler-MacFarland, Erich Seifritz, Christoph Hock, and Rudolf Stohler. "New aspects in the treatment of heroin dependence with special reference to neurobiological aspects." European psychiatry 17, no. 3 (2002): 163-166.	Discussion of Swiss heroin trials – not a systematic review
10	Seivewright, Nicholas, and Muhammad Z. Iqbal. "Prescribing to drug misusers in practice—often effective, but rarely straightforward." Addiction biology 7, no. 3 (2002): 269-277.	Not a systematic review
11	De Castro, Silvana, and Eduardo Sabaté. "Adherence to heroin dependence therapies and human immunodeficiency virus/acquired immunodeficiency syndrome infection rates among drug abusers." Clinical infectious diseases 37, no. Supplement_5 (2003): S464-S467.	Not a systematic review

12	Bammer, Gabriele, van den Brink, Wim, Gschwend, Patrick, Hendriks, Vincent, and Rehm Jürgen. "What can the Swiss and Dutch trials tell us about the potential risks associated with heroin prescribing?." Drug and Alcohol Review 22, no. 3 (2003): 363-371.	Not a systematic review
13	Carnwath, Tom. "Prescribing heroin." The American journal on addictions 14, no. 4 (2005): 311-318.	Not a systematic review
14	van den Brink, Wim, and Christian Haasen. "Evidence-based treatment of opioid-dependent patients." The Canadian Journal of Psychiatry 51, no. 10 (2006): 635-646.	Overview of treatment options – not a systematic review
15	Fischer, Benedikt, Eugenia Oviedo-Joekes, Peter Blanken, Christian Haasen, Jürgen Rehm, Martin T. Schechter, John Strang, and Wim van den Brink. "Heroin-assisted treatment (HAT) a decade later: a brief update on science and politics." Journal of Urban Health 84, no. 4 (2007): 552-562.	Not a systematic review
16	Prescription of injectable heroin for drug users. National Board of Health, Denmark, March 2008	Not a systematic review
17	Minozzi, Silvia, Laura Amato, Simona Vecchi, and Marina Davoli. "Maintenance agonist treatments for opiate dependent pregnant women." Cochrane Database Syst Rev 2 (2008).	Systematic review, but does not include studies of the intervention of interest.
18	Katz, Jessica G. "Heroin maintenance treatment: its effectiveness and the legislative changes necessary to implement it in the US." J. Contemp. Health L. & Pol'y 26 (2009): 300.	Not a systematic review
19	Lintzeris, Nicholas. "Prescription of heroin for the management of heroin dependence." CNS drugs 23, no. 6 (2009): 463-476.	Not a systematic review
20	Reuter, Peter. "Ten years after the United Nations General Assembly Special Session (UNGASS): assessing drug problems, policies and reform proposals." Addiction 104, no. 4 (2009): 510-517.	Not a systematic review
21	Reuter, Peter, and J. Anuary. Can Heroin Maintenance Help Baltimore? What Baltimore can learn from the experience of other countries." (2009). The Abell Foundation: Baltimore, MD.	Not a systematic review
22	Blanken, Peter, Wim van den Brink, Vincent M. Hendriks, Ineke A. Huijsman, Marjolein G. Klous, Elisabeth J. Rook, Jennifer S. Wakelin, Cas Barendrecht, Jos H. Beijnen, and Jan M. van Ree. "Heroin-assisted treatment in the Netherlands: History, findings, and international context." European Neuropsychopharmacology 20 (2010): S105-S158.	Overview of history, context, and evidence from the Netherlands – not a systematic review.
23	Demaret, Isabelle, André Lemaître, and Marc Ansseau. "L'efficacité du traitement assisté par diacétylmorphine (héroïne pharmaceutique) à l'étranger." Revue medicale de Liege 65, no. 12 (2010): 681-687.	Not a systematic review
24	Gowing L, Farrell MF, Bornemann R, Sullivan LE, Ali R. Oral substitution treatment of injecting opioid users for prevention of HIV infection. Cochrane Database of Systematic Reviews 2011, Issue 8. Art. No.: CD004145.	Systematic review, but does not include studies of the intervention of interest
25	MacCoun, Robert J., and Peter Reuter. "Assessing drug prohibition and its alternatives: A guide for agnostics." Annual Review of Law and Social Science 7 (2011): 61-78.	Not a systematic review
26	Praveen, K. Thyarappa, Fergus Law, Jacinta O'Shea, and Jan Melichar. "Opioid dependence." BMJ clinical evidence 2011 (2011).	Systematic review, but does not include studies of the intervention of interest
27	Uchtenhagen, Ambros A. "Heroin maintenance treatment: from idea to research to practice." Drug and alcohol review 30, no. 2 (2011): 130-137.	Overview of history and evidence on heroin-assisted treatment -- not a systematic review

28	Danet, Alina, Joan Carles March Cerdá, and Manuel Romero Vallecillos. "Los programas experimentales con heroína en la atención de la población drogodependiente." Salud y drogas 12, no. 1 (2012).	Literature review – not a systematic review
29	Petrushevska, Tatjana. "Heroin Maintenance Treatment-Are the Further Investigation Needed?." Macedonian Journal of Medical Sciences 5, no. 4 (2012): 453-461.	Not a systematic review
30	Heberlein, Annemarie, Lorenzo Leggio, Dirk Stichtenoth, and Hillemacher Thomas. "The treatment of alcohol and opioid dependence in pregnant women." Current opinion in psychiatry 25, no. 6 (2012): 559.	Literature review – not a systematic review.
31	Tetrault, Jeanette M., and David A. Fiellin. "Current and potential pharmacological treatment options for maintenance therapy in opioid-dependent individuals." Drugs 72, no. 2 (2012): 217-228.	Not a systematic review
32	van den Brink, Wimk. "Evidence-based pharmacological treatment of substance use disorders and pathological gambling." Current drug abuse reviews 5, no. 1 (2012): 3-31.	Literature review – not a systematic review
33	Ferri, Marica, Silvia Minozzi, Laura Amato, Alessandra Bo, and Marina Davoli. "Slow-release oral morphine as maintenance therapy for opioid dependence." Cochrane Database of Systematic Reviews 5 (2012).	Systematic review, but does not include studies of the intervention of interest.
34	Minozzi, Silvia, Laura Amato, Cristina Bellisario, Marica Ferri, and Marina Davoli. "Maintenance agonist treatments for opiate-dependent pregnant women." The Cochrane Library (2013).	Systematic review, but does not include studies of the intervention of interest.
35	Minozzi, Silvia, Laura Amato, Cristina Bellisario, and Marina Davoli. "Maintenance treatments for opiate-dependent adolescents." The Cochrane Library (2014).	Systematic review, but does not include studies of the intervention of interest.
36	Bell, James. "Pharmacological maintenance treatments of opiate addiction." British journal of clinical pharmacology 77, no. 2 (2014): 253-263.	Not a systematic review
37	Dennis, Brittany Burns, Leen Naji, Monica Bawor, Ashley Bonner, Michael Varenbut, Jeff Daiter, Carolyn Plater et al. "The effectiveness of opioid substitution treatments for patients with opioid dependence: a systematic review and multiple treatment comparison protocol." Systematic reviews 3, no. 1 (2014): 105.	Description of systematic review protocol
38	Garcia-Portilla, Maria Paz, Maria Teresa Bobes-Bascaran, Maria Teresa Bascaran, Pilar Alejandra Saiz, and Julio Bobes. "Long term outcomes of pharmacological treatments for opioid dependence: does methadone still lead the pack?." British journal of clinical pharmacology 77, no. 2 (2014): 272-284.	Selective review – not a systematic review.
39	Johansen, Birgitte Schepelern, and Katrine Schepelern Johansen. "Heroin: From Drug to Ambivalent Medicine." Culture, Medicine, and Psychiatry 39, no. 1 (2015): 75-91.	Anthropological analysis – not a systematic review.
40	Soyka, Michael, and Jochen Mutschler. "Treatment-refractory substance use disorder: Focus on alcohol, opioids, and cocaine." Progress in Neuro-Psychopharmacology and Biological Psychiatry 70 (2016): 148-161.	Narrative review – not a systematic review
41	Topcuoglu, Tuba. "Effectiveness of Prison-based Drug Treatment Programs: A Systematic Review of Meta-analyses." Addicta-The Turkish Journal on Addictions 3, no. 1 (2016): 110-124.	Systematic review, but does not include studies of the intervention of interest
42	Bell, James, Rob van der Waal, and John Strang. "Supervised injectable heroin: a clinical perspective." The Canadian Journal of Psychiatry 62, no. 7 (2017): 451-456.	Narrative review – not a systematic review.

43	Woody, George E. "Advances in the treatment of opioid use disorders." F1000Research 6 (2017).	Not a systematic review
44	Eibl, Joseph K., Kristen Morin, Esa Leinonen, and David C. Marsh. "The State of Opioid Agonist Therapy in Canada 20 Years after Federal Oversight." The Canadian Journal of Psychiatry (2017): 0706743717711167.	Overview of opioid agonist treatment in Canada – not a systematic review.
45	Uchtenhagen, Ambros. "The role and function of heroin-assisted treatment at the treatment system level." Heroin Addiction & Related Clinical Problems (2017); 19(2): 17-24	Not a systematic review