Research priorities for expanding access to methadone treatment for opioid use disorder in the United States: A National Institute on Drug Abuse Center for Clinical Trials Network Task Force report

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In the US, methadone treatment can only be provided to patients with opioid use disorder (OUD) through federal and state-regulated opioid treatment programs (OTPs). There is a shortage of OTPs, and racial and geographic inequities exist in access to methadone treatment. The National Institute on Drug Abuse Center for Clinical Trials Network convened the Methadone Access Research Task Force to develop a research agenda to expand and create more equitable access to methadone treatment for OUD. This research agenda included mechanisms that are available within and outside the current regulations. The task force identified 6 areas where research is needed: (1) access to methadone in general medical and other outpatient settings; (2) the impact of methadone treatment setting on patient outcomes; (3) impact of treatment structure on outcomes in patients receiving methadone; (4) comparative effectiveness of different medications to treat OUD; (5) optimal educational and support structure for provision of methadone by medical providers; and (6) benefits and harms of expanded methadone access. In addition to outlining these research priorities, the task force identified important cross-cutting issues, including the impact of patient characteristics, treatment, and treatment system characteristics such as methadone formulation and dose, concurrent behavioral treatment, frequency of dispensing, urine or oral fluid testing, and methods of measuring clinical outcomes. Together, the research priorities and cross-cutting issues represent a compelling research agenda to expand access to methadone in the US.

KEYWORDS
Access; methadone; opioid use disorder

ABSTRACT
In the US, methadone treatment can only be provided to patients with opioid use disorder (OUD) through federal and state-regulated opioid treatment programs (OTPs). There is a shortage of OTPs, and racial and geographic inequities exist in access to methadone treatment. The National Institute on Drug Abuse Center for Clinical Trials Network convened the Methadone Access Research Task Force to develop a research agenda to expand and create more equitable access to methadone treatment for OUD. This research agenda included mechanisms that are available within and outside the current regulations. The task force identified 6 areas where research is needed: (1) access to methadone in general medical and other outpatient settings; (2) the impact of methadone treatment setting on patient outcomes; (3) impact of treatment structure on outcomes in patients receiving methadone; (4) comparative effectiveness of different medications to treat OUD; (5) optimal educational and support structure for provision of methadone by medical providers; and (6) benefits and harms of expanded methadone access. In addition to outlining these research priorities, the task force identified important cross-cutting issues, including the impact of patient characteristics, treatment, and treatment system characteristics such as methadone formulation and dose, concurrent behavioral treatment, frequency of dispensing, urine or oral fluid testing, and methods of measuring clinical outcomes. Together, the research priorities and cross-cutting issues represent a compelling research agenda to expand access to methadone in the US.

Introduction
In the US, opioid overdose deaths are rising in the context of fentanyl use and the coronavirus 2019 (COVID-19) pandemic. Methadone treatment for opioid use disorder (OUD) is effective in reducing opioid morbidity and mortality, with more than 50 years of evidence. US methadone treatment capacity has not expanded proportionately with rising opioid overdose deaths, and not all patients who may benefit from methadone, a full agonist opioid medication, are able to access this treatment. The Drug Addiction Treatment Act of 2000 (DATA 2000) expanded access to medication-based treatment within the US by creating a pathway for medication treatment in office-based settings; to date, formulations of buprenorphine (a partial agonist opioid) are the only approved medications for OUD (MOUD) treatment under DATA 2000. DATA 2000 did not address the provision of methadone treatment outside of federally...
and state-regulated opioid treatment programs (OTPs) and did not increase access of methadone treatment within OTPs. Despite the increased number of OTPs in recent years due to expansion of the for-profit sector, there remains a shortage of methadone treatment that contributes to racial, gender, and geographic inequities in access to such treatment in the US.  

The COVID-19 pandemic and its associated social distancing and lockdown measures have created unprecedented challenges for the treatment of OUD. The crowding of patients within OTPs required rapid changes in the delivery system to reduce the risk of transmission of the virus that causes COVID-19. To mitigate the risk, the US Substance Abuse and Mental Health Services Administration (SAMHSA) and the Drug Enforcement Administration (DEA) relaxed restrictions on dispensing of methadone take-home dosing and allowed for the use of telemedicine for established patients receiving methadone. These COVID-19–related changes to the regulations governing methadone treatment have created opportunities to revisit the traditional ways of conducting methadone treatment and inspired thinking about alternative models for delivery of methadone. In response to COVID-19 disruptions, the rapid adaptation of US methadone treatment services, and the ongoing inequities in opioid agonist treatment access, the National Institute on Drug Abuse (NIDA) Center for Clinical Trials Network (CCTN) created the Methadone Access Research Task Force. The task force was asked to develop a research agenda to expand and create more equitable access to methadone for OUD. This research agenda was to include mechanisms that are available within and outside the current US regulations.

### Background and definitions

#### Current regulation of methadone treatment

In 1972 the US Food and Drug Administration (FDA) approved methadone treatment for OUD, and the passage of the Narcotic Addict Treatment Act in 1974 created the first federal law governing methadone for OUD. State and local governments have since placed additional regulatory requirements on methadone and, in 2000, federal regulatory oversight was transferred from the FDA to SAMHSA. Within the US, methadone for OUD may only be provided through SAMHSA-certified OTPs. OTPs are also regulated by the DEA. Methadone treatment for OUD comprises 3 basic components: (1) ordering or prescribing methadone, (2) administering or dispensing methadone, and (3) providing counseling and other psychosocial services. Medical providers (physician or advance practice providers such as physician assistants or nurse practitioners) are prohibited from using their DEA registration (license) to prescribe methadone for OUD, but they can prescribe methadone for chronic pain treatment as tablets. Without OTPs, methadone is ordered (not prescribed) for patients who are registered as enrolled in the OTP by staff medical providers and the medication is administered orally or dispensed to the patient by the OTP. In contrast, for office-based treatment under DATA 2000, formulations of buprenorphine for OUD are usually prescribed by a medical provider under their DEA registration, and it is then dispensed by a pharmacy for unobserved patient self-administration. Methadone administration refers to medication dosing at an OTP, directly observed by an OTP staff member, typically a nurse, while methadone dispensing refers to take-home doses provided to the patient by the OTP for patient self-administration. Each OTP has its own DEA registration, and methadone provision occurs under the DEA registration of the OTP, not the clinician’s DEA registration. Of note, buprenorphine administration and dispensing is allowed by OTPs but is less widely used.

Federal law requires an in-person medical evaluation prior to patient enrollment in an OTP. Upon enrollment, patients receiving methadone must return a minimum of 6 days a week for medication administration for at least the first 90 days of treatment. Patients are able to receive additional take-home doses if they meet specific requirements. Thus, they can receive one additional take-home dose at the second and third 90 days of treatment, after which they can receive up to 6 total take-home doses per week during the first year of treatment. After 1 and 2 years, they can receive 2 weeks and 1 month of take homes, respectively. States also have the authority to further restrict administration and dispensing policies. In March 2020, SAMHSA relaxed the methadone dispensing (take-home) allowance requirements in response to COVID-19. While the use of telemedicine was allowed for established patients in response to COVID-19, an in-person evaluation was still required for OTP enrollment and methadone initiation.

#### International regulatory approaches

Other nations have adopted different models of methadone treatment. In Canada, the UK, and Australia, methadone may be prescribed within addiction specialty or general medical (e.g., primary care) settings and the medication may be administered and/or dispensed at community pharmacies under a 3-party contract. Within these nations, the option to separate methadone prescribing, administration, and dispensing and psychosocial services allows OUD treatment to be integrated into care delivery systems for other chronic diseases. This approach to methadone treatment within Canada was associated with reduced mortality relative to individuals not receiving methadone, but research is needed to evaluate the implementation and impact of separating these 3 basic services or providing them outside of OTPs within the US.

#### Opportunities for innovation

Widespread integration of methadone treatment for OUD into treatment settings outside of OTPs would require modification of current US federal law; however, existing regulations do provide opportunities to extend some basic services beyond the traditional OTP. Current federal regulations...
allow for medication units, methadone “medical mainte-
nance,” and mobile units.\textsuperscript{30,32,37} These models are under-
used and understudied. The implementation of these
strategies require compliance with state and federal regu-
lations and in some cases may require OTP program-wide
exemptions from specific federal and state regulations.

Medication units are clinical locations (e.g., pharmacy,
health department, or Federally Qualified Health Center
[FQHC]), which may administer and dispense methadone
with appropriate DEA-approved safeguards for storage and
record keeping.\textsuperscript{30,32} Medication units may only administer
and/or dispense methadone to patients enrolled in an OTP
with an OTP-affiliated clinician’s order for methadone.\textsuperscript{30}
Medication units may also administer toxicology testing, but
current regulations prohibit a medication unit from provid-
ing in-person counseling services. The increasing availability
of telehealth services may provide novel opportunities to
integrate medication units and behavioral services as well as
to create remote systems for monitoring medica-
tion adherence.

In isolated instances, the methadone “medical main-
tenance” model provides methadone treatment to patients
with demonstrated clinical stability whose care is transferred
from an OTP to an office-based practice.\textsuperscript{38} For the metha-
done medical maintenance model, the office-based medical
provider prescribes and the pharmacist dispenses the medi-
cation. The methadone medical maintenance model includes
medication take-home dosing (up to 28 days), administra-
tion, and/or dispensing of the tablet form of methadone and
does not require concurrent behavioral treatment beyond
that provided by the office-based physician.\textsuperscript{38} These programs have historically operated under FDA Investigational
New Drug procedures or OTP program-wide exemptions to
federal regulations and remained limited in number.\textsuperscript{39}

There is a DEA mechanism to approve mobile units
(mobile OTPs or methadone medication units) if doing so is
considered consistent with public health and safety. Relatively few mobile units are currently functioning due to
regulatory requirements, and the DEA placed a moratorium
on new mobile units in 2007.\textsuperscript{37} In June 2021, the DEA
enacted new regulations that would eliminate the require-
ment for a mobile unit to obtain a separate DEA
registration.\textsuperscript{37}

Outside of current federal regulations, there are opportu-
nities to further integrate OTP services into community
pharmacies and make methadone available to patients via
prescription from OTP-affiliated clinicians, especially in
methadone treatment shortage areas such as most rural
communities. Two unique NIDA-funded pilot studies
obtained the necessary DEA exceptions and SAMHSA waivers (these regulatory exceptions are currently restricted to
these studies) to evaluate pharmacy dispensing and adminis-
tration of methadone to select OTP patients via electronic
prescriptions from OTP clinicians.\textsuperscript{40} One study was com-
pleted recently, enrolling 20 stable patients receiving metha-
done, and the treatment retention rate was 80% (16/20)
after 3 months.\textsuperscript{40} The DEA and SAMHSA approved the 2
trials and may be supportive of further work on pharmacy
integration of methadone for OUD.

Methods

Development of research priorities

The task force was initiated by the director of the CCTN
(BT) and a NIDA medical officer (DL), who invited a chair
(DAF). Task force members volunteered to participate fol-
dowing a notification of the CCTN Node Principal
Investigators of the creation of the task force and the oppor-
tunity for those who were interested to participate. This
resulted in a panel of 31 members (see Appendix 1) reflect-
ing the fields of addiction medicine, primary care internal
medicine, general psychiatry, addiction psychiatry, clinical
psychology, OTP leadership, NIDA program staff, health
care policy, and clinical research. The task force met weekly
between July and December 2020. Prior to the development
of the research priorities, the task force reviewed the history
of methadone provision within the US and the relevant
international literature on the effectiveness and safety of
methadone provision within and outside of the US OTP
model. Outside experts and relevant stakeholders presented
to the task force including patient advocacy through the
National Alliance for Medication Assisted Recovery and
Medication Assisted Recovery Support.

The task force considered research questions within and
outside of current federal regulations governing methadone
provision. For research conducted within current regula-
tions, the task force prioritized providing components of the
services of methadone treatment outside of OTPs (e.g.,
medication units and mobile units) but did consider oppor-
tunities within OTPs when aligned with the aim of expand-
ing and improving equity in methadone access. Research
questions outside of current regulations may require exemp-
tions (e.g., Controlled Substance Act research exemption).

The task force first identified a series of cross-cutting
issues to be considered across all research on expanding
access to methadone. Researchers should consider these
cross-cutting issues (Table 1) in their approach and study
design. The task force next identified research priorities
using a modified Zerhouni matrix to organize research ques-
tions within 3 levels of complexity.\textsuperscript{41} Research that could be
completed within the (1) short (1–2 years); (2) medium
(3–4 years); and (3) long (5+ years) term. Upon creation,
the draft document was shared with all task force members
and other stakeholders for input. Final priorities were agreed
upon by consensus and approved by all members.

Task force summary

Cross-cutting issues

Cross-cutting issues were organized into 4 domains: (1)
patient characteristics, (2) treatment characteristics, (3)
system and setting characteristics, and (4) methods of assess-
ment (Table 1). The patient characteristics domain includes
patient factors that may impact methadone access or
effectiveness (e.g., race/ethnicity, rurality, gender, comorbidities, or patient preference). The treatment characteristics domain includes variations in the dose of methadone, dispensing frequency as a function of stability, or the pairing of medications with other services (e.g., behavioral, or social services). The system and setting characteristics domain includes organizational differences in methadone treatment (e.g., pharmacy administration or telemedicine) and differences in the location where methadone treatment occurs (e.g., urban vs rural). The methods of assessment domain involve consideration of how study outcomes will be assessed (e.g., face-to-face or by telephone). Individual investigations do not need to incorporate all cross-cutting issues into a single design, but appropriate consideration of these issues will improve research methods and their impact.

Table 1. Cross-cutting issues impacting access to methadone for opioid use disorder.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Characteristic</th>
<th>Research decisions to be made</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Demographics</td>
<td>What are the study eligibility criteria?</td>
</tr>
<tr>
<td></td>
<td>Age, developmental stage, sex, race, sexual minorities</td>
<td>Is there a clinical reason methadone may be a better form of MOUD for the patient?</td>
</tr>
<tr>
<td></td>
<td>Comorbid conditions</td>
<td>Is there a clinical reason methadone may be a better form of MOUD for the patient?</td>
</tr>
<tr>
<td></td>
<td>Mood disorders, ADHD, PTSD, pain, HCV, HIV, injection-related conditions, other SUDs</td>
<td>How is patient stability operationalized?</td>
</tr>
<tr>
<td></td>
<td>New treatment episode vs treatment continuation</td>
<td>How will patient preferences be measured and included in study design?</td>
</tr>
<tr>
<td></td>
<td>Patient “stability”</td>
<td>What behavioral services will be provided?</td>
</tr>
<tr>
<td></td>
<td>Patient preferences</td>
<td>Are behavioral services provided in-person and/or using telehealth?</td>
</tr>
<tr>
<td>Treatment</td>
<td>Behavioral services</td>
<td>What social, medical, and psychiatric services will be provided?</td>
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<tr>
<td></td>
<td>Medication formulations</td>
<td>What methadone formulations and comparator medications will be used?</td>
</tr>
<tr>
<td></td>
<td>Level of treatment integration</td>
<td>How is treatment integrated into the setting? Is it integrated at the provider level or the office/clinic/ practice level?</td>
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<td></td>
<td>Quality of care, fidelity</td>
<td>How will process measures and fidelity be assessed?</td>
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<tr>
<td></td>
<td>Treatment location</td>
<td>Where are the various components of treatment provided?</td>
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<tr>
<td></td>
<td>Treatment structure</td>
<td>What are the key domains of treatment structure (i.e., dispensing frequency, urine monitoring, observed ingestion, face-to-face visits, flexibility, behavioral services) and how will they vary across study comparators?</td>
</tr>
<tr>
<td>System</td>
<td>Implementation</td>
<td>Which implementation science design is most appropriate for the research question?</td>
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<tr>
<td></td>
<td>Policy and reimbursement</td>
<td>What are the facilitators and barriers to implementation of methadone outside of OTPs?</td>
</tr>
<tr>
<td></td>
<td>Methods and location of medication administration and dispensing</td>
<td>How will regulatory policy or provider reimbursement need to change to conduct the research or implement the findings?</td>
</tr>
<tr>
<td></td>
<td>Methadone storage</td>
<td>How and where will methadone and/or comparator medications be administered/dispensed/prescribed/ordered (from OTP, pharmacy, FQHC, mobile unit, directly observed treatment, door-to-door delivery)?</td>
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<tr>
<td></td>
<td>Urban and rural</td>
<td>How will methadone be stored along the supply chain?</td>
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<tr>
<td></td>
<td>Care models (i.e., hub and spoke, stepped care)</td>
<td>Will the research take place in urban and/or rural settings? Will the interventions or findings be relevant to both urban and rural settings?</td>
</tr>
<tr>
<td></td>
<td>Telehealth</td>
<td>Will telehealth be part of the intervention?</td>
</tr>
<tr>
<td></td>
<td>Clinician training</td>
<td>What clinicians will be involved in patient care and what training will they need to provide methadone safely?</td>
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<tr>
<td></td>
<td>Stigma</td>
<td>How will OUD and MOUD stigma be assessed and addressed?</td>
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<tr>
<td></td>
<td>Public health, safety, diversion, and surveillance</td>
<td>How will surveillance for methadone or comparator medication diversion be conducted? How will the impact of increased access to methadone on untreated OUD in the community be assessed? How will the impact of increased access to methadone on fatal and nonfatal overdose in the community be assessed?</td>
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<tr>
<td></td>
<td>Disaster planning</td>
<td>What provisions are in place for threats to interruption of access to methadone or comparators due to disasters?</td>
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<tr>
<td></td>
<td>Confidentiality</td>
<td>How will patient confidentiality be handled vis a vis HIPAA and 42 CFR if applicable?</td>
</tr>
<tr>
<td>Assessments</td>
<td>Method of collection</td>
<td>How will baseline and follow-up assessments be obtained (face-to-face, email, telephone, computer)?</td>
</tr>
</tbody>
</table>

ADHD: Attention Deficit Hyperactivity Disorder; PTSD: Post Traumatic Stress Disorder; HCV: Hepatitis C Virus; HIV: Human Immune Deficiency Virus; SUD: Substance Use Disorder; FQHC: Federally Qualified Health Center; OUD: Opioid Use Disorder; MOUD: Medications for Opioid use Disorder.
**Research priorities**

The task force identified 6 research priorities to expand and create more equitable methadone access. Short-, medium-, and long-term research questions are presented for each research priority.

**Methadone in outpatient general medical and other outpatient settings**

Conduct research that uses outpatient general medical settings (e.g., office-based) and other outpatient settings to coordinate methadone treatment. The restriction of methadone in the US to federally regulated OTPs results in limited access to an FDA-approved and highly effective medication for OUD. Effectiveness and implementation research is needed on methadone treatment in general medical, mental health, and other outpatient settings. This research should prioritize in study design (e.g., site selection, study population, and recruitment) the cross-cutting issue of patient characteristics given racial, gender, and geographic inequities in methadone access within OTPs.

**Short term: 1–2 years**

- Conduct systematic or scoping reviews of research on the effectiveness and implementation of methadone treatment within general medical, mental health, and other outpatient settings. Within the US, this may include studies examining medication units, methadone medical maintenance, and mobile units. Internationally, this includes research using existing data from countries with greater integration of methadone treatment into general medicine and outpatient settings.
- Conduct mixed-methods research guided by implementation science frameworks on the barriers and facilitators of methadone treatment implementation within general medical and other outpatient settings. This research should include the perspectives of patients, office-based clinicians including those currently providing buprenorphine treatment, clinic staff, FQHCs, payers, health care administrators, pharmacy professionals, OTP professionals, and federal and state regulators. These studies can use existing research infrastructures such as practice-based research networks.

**Medium term: 3–4 years**

- Develop and pilot implementation interventions to address barriers and facilitators to implementing methadone treatment services in general medical and other outpatient settings.

**Long term: 5 or more years**

- Test the comparative effectiveness of various models of delivering methadone treatment services in general medical and other outpatient settings. Test implementation science interventions to address the barriers and facilitators and promote adoption of methadone treatment within general medical and other outpatient settings.

**Impact of treatment setting**

Conduct research to identify the impact of treatment setting (e.g., OTP, office-based, pharmacies) on patient outcomes across the OUD treatment cascade (treatment engagement, medication for OUD initiation, treatment retention, and remission). Methadone treatment for OUD is primarily located in specialty OTP settings, while buprenorphine is available in both general medical and specialty settings including an increasing portion of OTPs. Treatment settings vary widely in resources and structure, including the frequency of contact and monitoring that they are able to provide; provision of medical, psychiatric, behavioral, and social services; and ease of access. The 3 components of methadone treatment (ordering or prescribing, administering and/or dispensing, and psychosocial services) could occur all together or in separate locations. The setting where patients receive these services can potentially move between locations based on treatment stage and clinical response (e.g., hub and spoke models).

Methadone medical maintenance programs assume the medication prescribing, urine monitoring, and behavioral services for stable OTP patients (using a variety of criteria) who are transferred to these general medical or other outpatient settings. To date, no research in the US has been conducted whereby a methadone treatment episode is initiated in a general medical setting or other outpatient setting. Current regulations allow for methadone to be initiated in an acute care hospital if the patient is admitted for a condition other than OUD. In addition, under special conditions, methadone treatment can be initiated and administered daily in an emergency department or office-based setting for 72 hours as a bridge to OTP services; however, clinicians are often unaware of this allowance. Other settings to consider for methadone initiation include jails, prisons, mobile units, shelters/transitional housing, medically managed withdrawal facilities, and syringe service programs. Research is needed on the impact of these settings on outcomes across the OUD treatment cascade.

**Short term: 1–2 years**

- Conduct systematic or scoping reviews of research from the US and internationally on models that disaggregate the 3 components (ordering or prescribing, administering or dispensing, and provision of treatment services) of methadone treatment.
- Conduct systematic or scoping reviews of research from the US and internationally that compare the impact of the setting of methadone treatment services on patients initiating and patients stabilized on methadone.
- Conduct research on the association between treatment setting and methadone initiation and treatment retention using existing international databases.
• Conduct formative research on the implementation of existing medication units, methadone medical maintenance, and mobile units in the US. This may include expansion of current programs using special federal exemptions to facilitate methadone prescribing at OTPs and pharmacy administration and dispensing.\textsuperscript{40}

\textbf{Medium term: 3–4 years}

• Conduct observational studies using patient registries to examine treatment setting among new or stabilized patients.\textsuperscript{44}
• Create a network of research sites (e.g., hub and spoke) that can transfer care of patients receiving all forms of MOUD between general medical and other outpatient settings and OTPs in a bidirectional manner based on patient treatment stage and clinical response.

\textbf{Long term: 5 or more years}

• Conduct comparative effectiveness and implementation research to test the impact of setting of various components of methadone treatment on outcomes across the OUD treatment cascade.

\textbf{Impact of treatment structure}

Patients differ on a variety of clinical domains and may have low or high need for medical, psychiatric, behavioral, and social services during methadone treatment. The optimal medication administration and dispensing schedule may differ based on patient characteristics or treatment setting. Clinicians often use both formal and informal metrics to match a patient to a treatment plan. The accuracy and optimal method for patient–treatment matching in and outside of OTPs is not known. Research on the optimal method of patient–treatment matching and the role of patient preference/shared decision making is needed.

\textbf{Short term: 1–2 years}

• Conduct systematic or scoping reviews of research from the US and other countries on methods to assess patient’s need for structure and medical, psychiatric, behavioral, and social services during methadone treatment in outpatient general medical, specialty, and OTP settings.
• Conduct mixed-methods and expert consensus techniques (e.g., Delphi) to identify the cogent domains for measurement of patient need for structure and medical, psychiatric, behavioral, and social services during methadone treatment and their impact on OUD treatment outcomes across outpatient general medical, specialty, and OTP settings.\textsuperscript{45}

\textbf{Medium term: 3–4 years}

• Create research sites in general medical and other outpatient settings to study components of treatment structure (visit frequency; medication dispensing schedule; toxicology testing; medical, psychiatric, behavioral, and social services) with all MOUDs.
• Develop and validate strategies to assess patient need for treatment structure and medical, psychiatric, behavioral, and social services during methadone treatment in outpatient general medical, specialty, and OTP settings.
• Develop mechanisms to match patients to structure and medical, psychiatric, behavioral, and social services needs during methadone treatment in outpatient general medical, specialty, and OTP settings.

\textbf{Long term: 5 or more years}

• Test the predictive validity of the domains and methods developed to assess patient need for structure and medical, psychiatric, behavioral, and social services during methadone treatment in outpatient general medical, specialty, and OTP settings.
• Test the comparative effectiveness of different treatment structures and medical, psychiatric, behavioral, and social services during methadone treatment on OUD treatment outcomes in outpatient general medical, specialty, and OTP settings.
• Test the impact of patient–treatment matching strategies, based on predicted need for structure and medical, psychiatric, behavioral, and social services, during methadone treatment on OUD treatment outcomes in outpatient general medical, specialty, and OTP settings.

\textbf{Comparative effectiveness of medications}

A variety of MOUD are available, some of which are approved for use in the US. While the relative efficacy and effectiveness of medications have been studied both in the US and in other countries,\textsuperscript{46–48} there are limited data to optimize the matching of patients to MOUD types in outpatient settings.\textsuperscript{49} The task force did not reach consensus on the value of repeating comparative effectiveness trials of medications in the US context vs relying on research conducted in other countries. However, there are no US trials of methadone compared to extended-release formulations of buprenorphine or naltrexone conducted in general medical and other outpatient settings. There are also no US data on certain medications (e.g., slow-release oral morphine) available internationally. Extended-release injected or implanted formulations of buprenorphine or naltrexone could be advantageous for patients who have difficulty with frequent clinic visits or daily medication administration, although full opioid agonist treatment with methadone within office settings may result in greater retention. Finally, buprenorphine is the most widely available MOUD within the US, but limited data exist guiding treatment for patients not benefiting from buprenorphine treatment. The impact of transitioning patients from other MOUDs to methadone (e.g., “stepping up” to methadone following a trial of buprenorphine) in general medical and other outpatient settings is unknown. Research is needed on the impact of methadone compared to and following other MOUDs (e.g., stepped care) in general medical and other outpatient settings.
Short term: 1–2 years
- Conduct systematic and scoping reviews of the effectiveness of methadone compared to and following other MOUD (e.g., stepped care) in general medical and other outpatient settings.
- Conduct research on the impact of methadone compared to and following other MOUD (e.g., stepped care) in general medical and other outpatient settings using international databases.

Medium term: 3–4 years
- Create general medical and other outpatient research sites able to study the comparative effectiveness of MOUDs and the effectiveness of “stepping up” to methadone following initial MOUD treatment.

Long term: 5 or more years
- Test the comparative effectiveness of methadone vs other MOUD on OUD treatment outcomes in general medical and other outpatient settings. This could include traditional OTPs to encourage OTPs to provide the full spectrum of MOUD, including both dispensed and prescribed buprenorphine and injectable formulations of buprenorphine and naltrexone.
- Test the impact of transitioning patients to methadone not benefiting from treatment with another MOUD (e.g., buprenorphine) vs continuation of the MOUD on OUD treatment outcomes in general medical and other outpatient setting.

Optimal educational and support structure
Most health care workers in general medical and other outpatient settings have minimal to no experience providing methadone for OUD. Methadone has a unique safety profile that is important to understand when coordinating care and adjusting initial doses. Similarly, stigma toward patients with OUD, especially those receiving methadone, can be pervasive in health care, and some patients value the privacy and anonymity of office-based treatment and pharmacy settings. The implementation of research on methadone treatment in general medical and other outpatient settings will require trained clinicians who receive ongoing support. The impact of educational strategies and ongoing support systems (e.g., mentor networks) on perceptions of methadone safety, quality of care, clinical knowledge, skills, and patient outcomes are not known. Research on the optimal method of training and supporting general medical health care workers and health care systems on methadone treatment is needed as policy makers enact more flexible methadone regulation. ACGME Fellowship training in Addiction Medicine and Addiction Psychiatry require rotations with methadone treatment settings, and fellowship training should be supported to provide a cadre of expert clinicians both to lead treatment systems and to lead broad-based training efforts for general clinicians.50

Short term: 1–2 years
- Conduct systematic or scoping reviews of research on quality of care, knowledge, attitudes, skills, and stigma among health care workers as it pertains to methadone provided through general medical and other outpatient settings.
- Conduct mixed-methods research to assess quality of care, knowledge, attitudes, skills, and stigma of health care workers as it pertains to methadone provided through general medical and other outpatient settings. This research should include the perspectives of patients, office-based providers including those currently providing buprenorphine treatment, FQHCs, pharmacy personnel, OTP personnel, and federal and state regulators. These studies can use existing research infrastructures such as practice-based research networks.
- Conduct research using expert consensus techniques (e.g., the Delphi method) to identify the domains for measurement of quality of care, knowledge, attitudes, skills, and stigma of health care workers as it pertains to methadone provided through general medical and other outpatient settings.

Medium term: 3–4 years
- If more flexible methadone regulations are enacted, conduct pilot studies of interventions to improve the quality of care, knowledge, attitudes, and skills, and lessen stigma by health care workers for patients receiving methadone through general medical and other outpatient settings.

Long term: 5 or more years
- If more flexible methadone regulations are enacted, test the impact in general medical and other outpatient settings of methadone educational and support strategies for health care workers and health care systems on quality of care, effectiveness, safety, and stigma.

Benefits and harms of expanded methadone access
Regulatory restrictions on access to methadone are often predicated on concerns of diversion and public health safety. Therefore, it is important to simultaneously assess benefits and potential harms of expanded access to methadone to inform policy makers and provide public health guidance. While monitoring the impact of increasing methadone access on OUD treatment engagement, initiation, and retention, it is also important to monitor the impact on diversion, overdose, and opioid use. Research on both the benefits and harms of increasing access to methadone through general medical and other outpatient settings is needed.

Short term: 1–2 years
- Conduct systematic or scoping reviews of research on morbidity and mortality related to methadone exposure
Conduct observational studies using data from the surveillance strategies of the US or other countries. US data sources to consider (not exhaustive) include the following:

- American Association of Poison Control Centers National Poison Data System
- CDC Wonder, National Vital Statistics System and Overdose Data to Action
- DEA Automation of Reports and Consolidated Orders System and National Forensic Laboratory Information System
- Office of National Drug Control Policy Emerging Threats Committee
- SAMHSA Drug Abuse Warning Network
- State Prescription Monitoring Programs

- Conduct research in follow-up to the recommendations of 2004 CSAT Methadone Associated Mortality: Report of a National Assessment for more useful data to include improved access to and timeliness of data on diversion, overdose, and opioid initiation due to methadone.51
- Identify strategies to minimize bias in case definitions and surveillance (toxicology testing in fatal and nonfatal events) as it pertains to methadone-associated events.52

**Medium term: 3–4 years**

- Conduct rigorous epidemiologic surveillance on methadone diversion, nonfatal and fatal methadone overdose, and opioid initiation via methadone in addition to monitoring methadone treatment engagement, initiation, and treatment retention.
- Establish identified (with privacy protection) databases that include linkages across local, state, or federal data (e.g., prescription drug monitoring programs, medical examiner/coroner, EMT/emergency department, criminal justice, and OTP) to allow for tracking of risk for cause-specific morbidity and mortality in children and adults as a result of methadone exposure.

**Long term: 5 or more years**

- Integrate studies on the impact of increasing access to methadone through general medical and outpatient settings with those on methadone diversion, overdose, and opioid initiation.

**Summary and conclusions**

Methadone treatment for OUD is limited to OTPs in the US, and there is both a shortage of OTPs and geographic inequities in access to methadone treatment services.11,31 Research informing the expansion of methadone treatment services both within and outside of OTP regulations is needed. The NIDA Center for Clinical Trials Network Methadone Access Research Task Force identified 6 research priorities to expand and create more equitable access to methadone for OUD: (1) methadone in outpatient general medical and other outpatient settings; (2) impact of treatment setting; (3) impact of treatment structure; (4) comparative effectiveness of medications; (5) optimal educational and support structure; and the (6) benefits and harms of expanded methadone access. In addition to outlining these research priorities, the task force identified important cross-cutting issues for incorporation into research designs for each of the research priorities. These research priorities and cross-cutting issues form a research agenda for the expansion of methadone access within the US.

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**Author contributions**

CCTN conceived of the Methadone Access Research Task Force and DF chaired the task force. All task force members, including all authors, contributed to the development of the research agenda. PJ drafted all initial commentary. All authors contributed to the writing of the manuscript.

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