The U.S. is in the midst of an unprecedented opioid overdose epidemic. In 2014, of the 47,055 drug overdose deaths in the U.S., 28,647 (61%) involved a prescription or illicit opioid. The public health harms related to opioid use are not limited to overdose deaths, as rising rates of emergency department visits, hepatitis C and HIV infections, and neonatal abstinence syndrome, among others, represent different facets of the opioid epidemic. At the same time, millions of Americans struggle with pain that interferes with many aspects of life, including their physical and mental health, work productivity, and ability to engage in social activities.

In an effort to reverse the opioid overdose epidemic and transform pain treatment in the U.S., the U.S. Department of Health and Human Services (HHS) launched its Opioid Initiative in March 2015 followed by the National Pain Strategy in March 2016. The Initiative employs high-impact interventions to: 1) improve opioid prescribing practices; 2) expand access to medication-assisted treatment (MAT) for opioid addiction; and 3) increase the use of naloxone to reverse opioid overdoses. In complement, the National Pain Strategy outlines the federal government’s first coordinated plan to reduce the burden of chronic pain in the U.S. and provides a roadmap toward achieving a system of care in which all people receive high quality, evidence-based pain care.

As part of this ongoing work, HHS completed a portfolio of the research on pain and on opioid misuse and overdose funded or conducted by HHS and identified the most pressing opportunities in these areas. This brief provides a synthesis of the HHS research portfolio, as well as future research opportunities. The complete research portfolio can be found here.

**Research to Track the Epidemic**

HHS agencies are engaged in a range of public health surveillance and epidemiological research activities to track pain treatment trends, opioid misuse, addiction, and overdose, and pain treatment, recognize emerging trends, and identify risk and protective factors. These efforts guide our actions to address the opioid epidemic.

The National Institutes of Health (NIH) is funding research to identify predictors of long-term opioid use and to develop methods for early identification of patients at increased risk for opioid-related harms. The U.S. Food and Drug Administration (FDA) is requiring manufacturers of extended-release/long-acting opioids to conduct a series of studies to characterize the serious risks of misuse, abuse, hyperalgesia (heightened sensitivity to pain), addiction, overdose, and death associated with long-term use of these medications.
HHS agencies also are involved in research to identify geographic, demographic, and individual-level risk factors for opioid abuse and overdose. The Centers for Disease Control and Prevention (CDC) is conducting research to assess changing patterns of opioid use, including examining prescribing and mortality trends at the regional level and identifying the characteristics of counties with patterns of high-risk opioid prescribing. The HHS Office of the Assistant Secretary for Planning and Evaluation (ASPE) is conducting research to characterize how patient behaviors such as receiving opioid prescriptions from multiple prescribers and pharmacies predict opioid misuse and overdose outcomes.

To address recent concerns around rising rates of injection drug use and associated health consequences, NIH is also funding research to identify factors that accelerate or inhibit transition from oral prescription opioid use to injection drug use. ASPE and CDC are collaborating to examine trends in non-oral use, including injection, of prescription opioids among individuals being admitted to substance abuse treatment programs. Given the recent increases in heroin and illicit fentanyl use, HHS agencies are also engaged in research to better understand the populations and risk factors associated with using these illicit opioids.

Finally, HHS is tracking trends in the use of MAT for opioid addiction and naloxone to reverse overdoses. The Centers for Medicare and Medicaid Services (CMS) is partnering with several states on research to characterize how buprenorphine is being prescribed in Medicaid. The Health Resources and Services Administration (HRSA) is conducting an analysis of state and local efforts to promote MAT access in rural areas, and the Substance Abuse and Mental Health Services Administration (SAMHSA) is tracking naloxone trends at the state and local level.

**Research to Understand Pain and Opioid Addiction**
Understanding genetic, physiological, and environmental factors that contribute to pain and addiction are fundamental to prevention and the development of new, more effective treatments.

**Pain-related research**
NIH is funding critical research to understand the fundamentals of pain, including identifying the molecular pathways and genetic regulation of pain and opioid signaling, the role inflammation plays in the transition from acute to chronic pain, biomarkers for pain conditions, and how neural hypersensitivity induced by repeated activation of pain signals in the body are associated with the development of chronic pain. NIH is also funding research to identify biological and psychological factors that put people at greater risk for chronic pain.
Opioid addiction-related research
NIH is funding research to identify the genetic mechanisms underlying an individual’s response to opioids and risk for opioid addiction, including the rewarding and aversive effects of opioids. In addition, NIH is funding research to understand the neurobiological and brain-related changes that mediate opioid use disorders. Finally, NIH is supporting research to identify neuroimaging and physiological biomarkers to help determine who will most likely benefit from and respond to different MAT medications.

Research on New Treatments for Pain, Opioid Addiction, and Opioid Overdose Reversal
There is a pressing need to encourage the development of new pain treatments; especially treatments with reduced risk for misuse, as well new treatments for opioid addiction and overdose reversal.

Pain treatments
FDA is partnering with external stakeholders to identify the best pain measures and clinical study designs to use in clinical trials for common conditions such as chronic low back pain, osteoarthritis, diabetic peripheral neuropathy, and fibromyalgia—a critical step to help treatment developers bring new treatments to patients more quickly.

NIH is supporting research to develop the next generation of pain treatments, including new compounds that work in different ways and on different brain receptors than the currently available prescription opioids. Initial studies indicate these new compounds can induce strong pain relief without producing tolerance or dependence. NIH is also funding novel treatments for pain that use tissue engineering and regeneration and infrared laser light to inhibit pain, as well as research on the effectiveness of various forms of brain stimulation for chronic pain treatment.

FDA and NIH have also supported the development of abuse-deterrent formulations of opioid analgesics. To date, FDA has approved six opioid analgesics with abuse-deterrent properties and has published guidance on evaluation and labeling requirements for abuse-deterrent products. FDA is requiring manufacturers of these products to conduct studies to assess the impact of their products in the real world. The recommended approach to these assessments have been captured in an guidance for industry, Abuse-Deterrent Opioids — Evaluation and Labeling.

Opioid addiction treatments
To facilitate the development of new opioid addiction products, FDA is working to improve the appropriate design and analysis of clinical trials to demonstrate the safety and effectiveness of opioid addiction treatments. FDA and NIH also are engaged in efforts to identify new ways to collect the data needed to support appropriate study endpoints for opioid addiction treatments. These are important steps in supporting the development of new treatments.
NIH is studying promising treatments, including funding several projects to develop vaccines directed against opioids and research to examine if the addition of other currently available prescription drugs in combination with current MAT medications improves outcomes for people with opioid addiction. In addition, NIH is funding research on the use of brain stimulation for the treatment of individuals with both pain and opioid addiction.

**Opioid overdose reversal treatments**
HHS has made significant strides in quickly bringing new opioid overdose reversal drugs to market with the approval of the naloxone autoinjector Evzio in April 2014 and the intranasal naloxone product Narcan Nasal Spray in November 2015. In addition, there is significant interest from stakeholders for over-the-counter (OTC) naloxone products. FDA has laid out the regulatory requirements for OTC naloxone and has been in discussions with interested manufacturers. FDA is also producing some of the information, including parts of labeling that could be used to support OTC naloxone.

**Research to improve clinical practice**
Conducting research to identify effective clinical practice interventions that improve pain treatment and reduce opioid misuse and overdose, and bringing them to scale are essential to reversing the opioid overdose epidemic. HHS research in this area spans from educational activities to guideline adoption to testing insurer strategies designed to ensure proper opioid prescribing.

**Clinical practice interventions for pain treatment**
Surveys of health care providers indicate they receive little training on pain management, and significant gaps in education in health professional schools have been identified. To help address these gaps, NIH has funded collaborative pain research initiatives at 11 Centers of Excellence in Pain Education (CoEPEs) to act as hubs for the development, evaluation, and distribution of pain management curriculum resources for medical, dental, nursing and pharmacy schools.

Testing new ways to provide pain treatment for common pain conditions is also a top priority for HHS. Agency for Healthcare Research and Quality (AHRQ) is funding research to compare the benefits of using early physical therapy in combination with medication management for patients with acute low back pain in primary care. FDA is funding a study designed to reduce the long-term use of opioids following surgery by identifying patients at highest risk of long-term, high dose opioid use and employing an opioid-sparing educational intervention to reduce opioid use. In addition, NIH is funding research to compare multi-disciplinary versus standard pain treatment in the primary care setting.

Research on how best to provide non-medication pain treatment is key to reducing an over-reliance on opioid medications. NIH is funding projects to determine the benefits of treatments such as cognitive behavioral therapy, acupuncture, spinal manipulation, and massage, as well as mind-body approaches like mindfulness meditation and yoga.
CDC is examining the uptake and impact of its recently released Guideline for Prescribing Opioids for Chronic Pain and funding research to determine the effectiveness of providing clinicians with real-time feedback on the potential misuse of prescription opioids through electronic alerts in medical record systems. Finally, CDC and CMS are studying how insurance strategies such as medication management, patient review and restriction programs, and other benefit design strategies impact opioid prescribing and health outcomes.

**Clinical practice interventions for opioid addiction treatment**

Although access to and receipt of MAT has increased, gaps remain in our understanding of best practices across different practice settings and in different patient populations.

NIH is funding research to characterize the factors that influence successful implementation of MAT in primary care, to implement collaborative care models that initiate buprenorphine treatment in the emergency room and coordinate with primary care, and to explore the use of mobile health and web-based patient support tools to improve treatment retention and outcomes.

Increasing MAT in rural areas is particularly needed. AHRQ is funding a series of research grants to implement and test solutions to overcoming barriers to MAT implementation in primary care practices in rural areas of the U.S. ASPE is conducting research to identify the best practices, barriers, and facilitators relevant to using telehealth to detect and manage behavioral health conditions, including opioid addiction, in rural areas. NIH has partnered with the Appalachian Regional Commission to offer services planning research grants specific to opioid injection drug use and its adverse health consequences in Appalachia. Additionally, CDC is funding 3 to 5 state health department-led demonstration projects on HIV prevention and preparedness, including providing MAT, in rural areas with high rates of injection drug use.

**Research to evaluate the impact of policy initiatives**

Identifying effective policies to improve pain treatment and reduce opioid misuse and overdose and working with decision-makers to implement them is key to the opioid crisis response.

**Opioid prescribing**

CDC is funding research to assess the impact of pill mill laws in multiple states, including the effect of these laws on high-risk patients, prescribers, and pharmacies. CDC is also conducting studies to determine the impacts of different aspects of prescription drug monitoring programs (PDMPs), including prescriber mandates, proactive reporting, and real-time data reporting.

An outstanding policy question that is important for advancing comprehensive pain treatment is whether and how insurance programs cover non-opioid pain treatments. ASPE, in partnership with CDC, NIH, and CMS, is funding an analysis of current insurance coverage policies for non-opioid pain treatments. This information will help inform future policy efforts and serve as the foundation for future research studies.
Medication-assisted treatment
The Substance Abuse and Mental Health Services Administration (SAMHSA) is evaluating the state of MAT through a cross-site comparison of MAT programs that differ in critical ways such as services offered, geographic location, and payment structures. SAMHSA is also funding an evaluation of the effectiveness of training and technical assistance provided to its MAT-Prescription Drug and Opioid Addiction grantees.

CDC is funding a longitudinal evaluation of MAT across different practice settings to inform which policies and practices can be scaled up to achieve population level impact. CDC is also funding an evaluation to determine the impact of co-locating hepatitis C treatment in an opioid addiction treatment environment. Finally, ASPE is planning an evaluation of the forthcoming final rule that will raise the limit on the number of patients to whom qualified physicians can prescribe buprenorphine for opioid addiction treatment.

Naloxone overdose reversal
CDC is conducting an evaluation of the 11 states funded through SAMHSA’s Grants to Prevention Drug/Opioid Overdose-Related Deaths program in order to describe and understand the scope and impact of the program on overdose deaths, identify how program effectiveness may vary among different sub-populations and settings, and to increase understanding of the barriers and facilitators to program implementation. In addition, SAMHSA is conducting research to identify how state and local policies expanding naloxone access are impacting outcomes.

Next Steps
As part of compiling our research portfolio inventory, HHS identified a number of high priority research opportunities – areas where research is not currently underway or where some research is occurring but more is urgently needed. HHS is now investing new resources to address these priority opportunities. Specifically, we will launch efforts to support more than a dozen new studies in 2016 and will be able to undertake additional efforts if the President’s FY 2017 request is enacted. These efforts will help to advance future policy and programmatic initiatives and advance our goals of improving pain treatment and reducing opioid misuse, addiction, and overdose.

New research to track the opioid epidemic will consist of studying the causal pathways of prescription drug misuse and overdose, including the transition from prescription opioid misuse to heroin use, examining prescription opioid misuse and heroin use among American Indian/Alaska Native populations, and studying how pain is being treated in the U.S. and the economic costs associated with its treatment. New foundational research will focus on identifying the people with pain who are most likely to benefit from opioid treatment and those most likely to experience opioid-related harms.
HHS is also investing in **research on new treatments**. This includes investigating the ability of different naloxone formulations to reverse fentanyl and other high-potency opioid overdoses, studies assessing the effectiveness of multidisciplinary pain care treatment, and a rigorous review of the scientific evidence for non-opioid pain treatments. **New research to improve clinical practice** will comprise examining acute opioid prescribing practices in order to reduce the amount of leftover, unneeded medication, and developing and validating clinical tools to assess patient risk. Finally, new **research to evaluate policy initiatives** will consist of studying coverage policies for and access to MAT and related behavioral health services, and evaluating the impact of state Good Samaritan laws.

In addition to these new investments in research, HHS identified several priority research opportunities that would be funded under the President’s fiscal year 2017 budget request. Opportunities consist of studying insurance reimbursement strategies that incentivize clinicians to provide MAT for opioid addiction; examining how best to implement MAT services across different health system and practice settings among different patient populations; research to understand how best to provide pain and opioid misuse education to healthcare professionals, and conducting evaluations to determine the impact of expanding naloxone distribution.