Rapid Review of Opioid Overdose Prevention

Research Priorities and Investments

Report to the NCIPC Board of Scientific Counselors

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Division of Unintentional Injury Prevention
National Center for Injury Prevention and Control
Centers for Disease Control and Prevention

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Purpose of the review

Timely, high quality, and impactful research is needed to address the burgeoning opioid epidemic in the United States. CDC conducts research to assess public health burden, identify risk and protective factors, develop and evaluate preventive interventions, and promote widespread adoption of effective strategies. The National Center for Injury Prevention and Control (NCIPC) established research priorities to address opioid overdose prevention (Table 1) in 2015. To assess progress in addressing these priorities, the Division of Unintentional Injury Prevention (DUIP) conducted a review of activities, short-term outputs, and long-term outputs associated with intramural and extramural research from 2012 to 2018. Given the need to obtain input quickly with the expanding epidemic and increase in budget to address it, DUIP developed key questions to guide a "rapid" review of our research priorities and activities, generated a logic model, and summarized overall progress with a high-level perspective. NCIPC is soliciting input and recommendations from the NCIPC Board of Scientific Counselors (BSC) to consider progress in addressing the research objectives, and determine need and provide recommendations for updating the agenda to address the evolving opioid epidemic.

Key questions to guide the review

DUIP leadership identified key questions to help guide a rapid review of the NCIPC intramural and extramural research portfolio addressing opioid overdose prevention. These questions are to be considered by the NCIPC Board of Scientific Counselors (BSC) in providing recommendations to NCIPC on needed updates to opioid research priorities.

Question 1: To what degree have the Center's intramural and extramural research projects addressed the established opioid research priorities?

Question 2: Are the research priorities currently comprehensive enough to address the ongoing and changing epidemic?

Question 3: Is there a need to update the research priorities due to changes in the epidemic, Center priorities, and need for Center/Agency coordination? If so, what topics might be of highest priority to address? What is the correct balance of maintaining "old" priorities to establish a critical mass of research, and establishing "new" priorities to move the field forward?

Logic model for the review

To assist in addressing the review questions, DUIP developed a logic model to outline the inputs, activities, short-term outputs, and long-term outputs (see Figure 1).

Figure 1: Inputs, activities, short-term outputs, and long-term outputs

Inputs	Activities	Short-term Outputs	Long-term Outputs
• Injury Center research priorities • Funding • Strategic frameworks • Inter-agency agenda setting • Data on the nature of the epidemic	• Extramural research notices of funding opportunity (NOFO) • Intramural concept proposals and research agenda planning	• Funded extramural research projects • Staffed intramural research projects	• Publications and other products that can support targeting and implementation of strategies to prevent and reduce opioid overdose

A summary of inputs, activities, short-term outputs, and long-term outputs is provided next. Following this description, contextual information is provided to describe the evolving nature of the opioid overdose epidemic, and efforts within the Center and Agency to coalesce priorities and activities to address it.

Inputs

In 2015, NCIPC established internal workgroups to identify priorities in each of the NCIPC focus topic areas to guide intramural and extramural research.[1] NCIPC intended for the priorities to guide the Center in identifying solutions for emerging issues, encouraging innovative research, creating more targeted research priorities that will help grow a critical mass of research for achieving impact, integrating NCIPC's extramural and intramural research, and focusing CDC's public health expertise. The priorities were established as a "living document", with the understanding that priorities and guiding questions would change to meet the needs of the injury prevention community. The goal was to establish impact or progress within 3 to 5 years. The full research priorities document is available at: https://www.cdc.gov/injury/researchpriorities/index.html.

NCIPC developed the opioid research priorities to support the existing DUIP strategic framework at that time to address opioid overdose (see Table 1). In 2015, this strategic framework had three pillars: (1) Improve data quality and track trends to monitor actionable changes in the epidemic, (2) Strengthen state efforts by scaling up effective public health interventions, and (3) Supply health care providers with data, tools, and guidance for evidence-based decision making to improve patient safety and public health. Since that time, the strategic framework has been revised to include five pillars: (1) Conduct surveillance and research, (2) Build state, local, and tribal capacity, (3) Support providers, health systems, and payers, (4) Partner with public safety, and (5) Empower consumers to make safe choices.

Strategic frameworks and research priorities are influenced by surveillance and programmatic data informing the nature of the epidemic, the amount and structure of appropriations for funding, as well as by interagency agenda setting activities to ensure efforts are complementary and to reduce duplication.

[1] Intramural research is identified as research conducted by CDC staff or solicited through contracting mechanisms and conducted under the direction of CDC. Extramural research is identified as research conducted by outside research investigators funded through grant or cooperative agreement assistance mechanisms (typically university-based).

Table 1: Injury Center research priorities on opioid overdose, 2015

FORMULARY MANAGEMENT: Evaluate the impact of insurer mechanisms and pharmacy benefit manager strategies to change prescribing behavior, inappropriate use of controlled substances, and patient outcomes.
• Which interventions change prescribing behaviors most effectively? • Which interventions are most cost-effective? • What are the effective ways state health departments can engage insurers and pharmacy benefit managers to foster adoption of these interventions?
PDMP/POLICY: Evaluate the impact of state policies and strategies that facilitate PDMP use, improve prescribing practices, educate patients, and encourage treatment and overdose response.
• What are the impacts of innovated, untested policies and strategies at the state level on prescribing rates and prescription or illicit drug misuse, abuse, and overdose? • What are the potential unintended consequences? • What are the impacts of harm-reduction strategies on drug overdose? • Which PDMP strategies enhance use and produce the greatest impacts? • What are the cost implications and cost savings of identified policy changes? • How can communications campaigns influence prescribing and opioid use?
RX TO ILLICIT: Identify factors that increase risk for prescription drug-related mortality, and identify risk and protective factors related to the co-use of prescription opioid pain relievers and heroin.
• How can PDMP, coroner, medical examiner, and law enforcement data be used to identify risk and protective factors for drug overdose? • What are the patterns of co-use of prescription opioids and heroin, injection of opioids, and overdose? • Does opioid pain reliever prescribing increase risk for heroin overdose?
CLINICAL CARE: Evaluate adoption, implementation, and impact of clinical practice guidelines, clinical decision supports, and coordinated care plans within primary care practices in health systems.
• What systems-level translation and improvement strategies can enhance adoption and effective use of recommended practices? • What are the clinical decision support needs, barriers, and effective approaches to promoting guideline adherence in primary care? • What factors facilitate adoption of coordinated care plans in health systems? • What are the patient and health system impacts of guideline, clinical decision support, and coordinated care plan implementation?

Activities

DUIP conducted a full systematic review of all extramural research solicited through funding announcements and funded through grants and cooperative agreements from 2012 to 2018. Given the need to conduct a more "rapid" review, DUIP pulled a sample of intramural research conducted since 2014 to highlight how intramural activities complement extramural activities within the research priority areas. This sample reflects only a portion of our intramural work, and is not meant to represent the full catalogue of intramural activities during this time.

Extramural research. NCIPC issues calls for proposals from the field to conduct extramural research through Notices of Funding Opportunities (NOFOs). Table 2 summarizes the NOFOs released that have included the opioid research priorities. The research priorities addressed by each NOFO is indicated in the right hand column – in many cases, NOFOs were intended to support research across multiple priority areas. NOFOs for individual cooperative agreements or grants dating back to 2012 have been listed, given that DUIP's strategic framework was in place prior to 2015, and this framework drove the development of the research priorities. Examining NOFOs dating back to 2012 also allows for a more thorough examination of funded extramural research to benchmark progress, and provides enough time to include products that take time to mature (e.g., scientific publications). Projects funded under the 2012 and 2014 NOFOs (and supplements) for the Injury Control Research Centers are included to represent contemporary ICRC research.

The NOFOs have supported three types of funding mechanisms: grants, cooperative agreements, and research centers. Some NOFOs for individual grants and cooperative agreements have focused solely on opioid overdose. In addition, broader focused Research Center grants have allowed for research in any of the NCIPC topic areas, including opioid overdose.

NCIPC does not have a specific funding line dedicated to support "research", other than the Injury Prevention Research Center funding line. Funding for other types of research is "set aside" from the general appropriation funding lines to ensure the generation of evidence that can directly support state public health injury prevention programmatic efforts. Historically, individual grants and cooperative agreements for opioid research have been funded through the "Injury Prevention Activities" funding line. However, the new opioid funding line offers new opportunities to generate evidence to support opioid-focused efforts.

Intramural research. NCIPC uses several mechanisms for intramural research planning. First, staff members within the Health Systems and Trauma Systems Branch (the branch in which the opioid work resides) work together to develop a cohesive intramural research agenda, in which activities to be conducted are outlined to support the NCIPC Research Priorities and newly emerging needs – often identified through state program work. This research agenda is regularly updated. Second, NCIPC hosts a module on SharePoint that serves as a one-stop-shop for Project Initiation Review for intramural projects that do not require external funding (e.g., secondary data analysis projects). This module is used by staff to seek approval for initiating a new project concept, and captures all relevant information to seek project approvals, with built-in workflows to route the approval from supervisors. This system offers a check to ensure that concepts pursued are high quality, and are consistent with research priorities. Finally, each year DUIP leadership present plans for allocation of funds to the NCIPC Office of the Director, including all extramural activities that require funding from surveillance to program to research. This "budget planning" activity is directed to ensure that funding proposals are high quality and consistent with research priorities.

Table 2: Notices of all extramural research funding opportunities addressing opioid overdose, 2012-2018

FY	Title	Scope	Priority
Individual Cooperative Agreements/Grants			
2012	Research to Prevent Prescription Drug Overdoses (RFA-CE-12-007)	Conduct research to evaluate novel approaches to drug overdose prevention engaging professionals from a wide spectrum of disciplines. Support projects that evaluate Medicaid, workers' compensation, or other state-run health plans; drug utilization review; pill mill legislation; policy/environmental change; PDMPs; or other system/policy change.	Formulary PDMP/Policy Clinical
2014	Research to Prevent Prescription Drug Overdoses (RFA-CE-14-002)	Conduct research to assess the impact of selected policies and administrative practices on the inappropriate prescribing or abuse of prescription opioid analgesics. Support projects that either evaluate current pill mill legislation or formulary management and benefit design strategies used by public or private insurers and pharmacy benefit managers.	Formulary PDMP/Policy
2014	Research on Integration of Injury Prevention in Health Systems (RFA-CE-14-004)	Conduct research that informs the link between public health and clinical medicine. Support projects that develop the evidence base for clinical preventive services in the area of prescription drug overdose, or investigate models for partnership between hospitals and state/local health departments in designing community needs assessments and improvement plans that incorporate injury prevention.	Clinical
2016	Research on Prescription Opioid Use, Opioid Prescribing, and Associated Heroin Risk (RFA-CE-16-003)	Conduct research to identify protective and risk factors that could enhance public health efforts to reduce morbidity and mortality related to heroin use and overdose. Support projects investigate the patterns of prescription opioid pain reliever (OPR) use and misuse, and initiation of heroin use during and/or after OPR misuse; and investigate how and under what circumstances OPR prescribing practices and policies are related to heroin initiation and overdose.	Rx to Illicit Clinical
2018	Research to Evaluate Medication Management of Opioids and Benzodiazepines to Reduce Older Adult Falls* (RFA-CE-18-004)	Conduct research to evaluate the effectiveness of medication tapering and/or discontinuation strategies to reduce falls and injury among older adults. Support projects that advance knowledge about how to improve prescribing for medications in which the risks may outweigh the benefits, contributing to falls, overdose, and other injuries.	Clinical
2018	Research Grants for the Primary or Secondary Prevention of Opioid Overdose (RFA-CE-18-006)	Conduct research to develop and pilot or rigorously evaluate novel primary or secondary prevention interventions to prevent opioid overdose. Support projects that evaluate strategies that integrate public health and public safety, enhance linkage to treatment, improve prescribing behavior, address modifiable risk and protective factors related to co-use of prescription opioids and heroin, involve employers, and address social determinants.	Formulary PDMP/Policy Rx to Illicit Clinical
Center Grants			
2014	Grants for Injury Control Research Centers (RFA-CE-12-001; RFA-CE-14-001)	Support research centers that conduct high quality research and help translate scientific discoveries into practice for the prevention and control of fatal and nonfatal injuries, violence, and related disabilities. Two of the research projects must address one of NCIPC's current research focus areas (including prescription drug overdose) or address high burden injury.	Formulary PDMP/Policy Rx to Illicit Clinical

* Primarily assigned to older adult falls research priority

Short-term Outputs

In response to the NOFOs issued, NCIPC has funded 14 research cooperative agreements and 6 research centers that address opioid overdose priorities. Note that the Fiscal Year 2018 NOFOs do not yet have projects awarded to describe.

Table 3 and Figures 2 through 4 illustrate the funded projects, principal investigators, institutions, funding amounts, and priority areas addressed. In one case, one award was funded through an Interagency Agreement with funds coming to CDC from the National Institute on Drug Abuse, National Institutes of Health, illustrating how the two HHS operating divisions have collaborated to leverage funds to support high priority projects.

Recently, NCIPC began an initiative to track intramural and extramural research projects and their outputs systematically through a Research Priorities Database and data visualization platform using Tableau. The figures included visualize data currently present in the database.

A narrative summary of how the extramural research projects have addressed each priority is provided next, with references to findings from publications identified when available (see the long-term outputs section for the specific publications referenced).

Research Priority: Evaluate the impact of insurer mechanisms and pharmacy benefit manager strategies to change prescribing behavior, inappropriate use of controlled substances, and patient outcomes.

Since 2012, the Injury Center has issued three funding opportunity announcements that solicit research to evaluate formulary management in Medicaid or Worker's Compensations. Other topics solicited for research within these announcements focused on evaluation of state policies, including prescription drug monitoring programs (PDMP) and pain clinic legislation, and cross over with other NCIPC Research Priority areas. Seven projects have been funded in response to two of these announcements (RFA-CE-12-007, RFA-CE-14-002); the other announcement is recent and projects have not yet been awarded (RFA-CE-18-006). Of the seven already funded projects, four specifically focus on formulary management.

One project in North Carolina (PI: Asheley Skinner, UNC-Chapel Hill) assessed changes in opioid use and overdose after implementation of a North Carolina Medicaid lock-in program (a program that designates a provider/pharmacy for prescriptions). Contextual research associated with this project in 2014 found that although lock-in programs were present in 46 Medicaid programs, the characteristics of these programs varied widely and there was little peer-reviewed research investigating effectiveness (Roberts et al. 2014). Findings of the current project help to fill that gap and suggest that, relative to the period before enrollment in the lock-in program, enrollment in the lock-in program reduced the odds of opioid claims, reduced the monthly number of opioid prescriptions, reduced the number of pharmacies utilized by patients, and reduced monthly Medicaid expenditures (Skinner et al. 2016). Further research from this project identified areas for lock-in program improvement to mitigate interference with access to health care and treatment (Werth et al. 2014) and suggested heterogeneity in patient response to lock-in programs that may inform program modifications to improve their effectiveness (Naumann et al. Pharmacoepidemiology and Drug Safety. 2018). Other project analyses discovered that some program enrollees were circumventing lock-in programs by obtaining care and opioid prescriptions using out-of-pocket payments (Roberts et al. 2016) and that morphine milligram equivalents actually increased when patients were enrolled into the program (Naumann et al. Drug and Alcohol Dependence. 2018).

The second project (PI Andrew Mulcahy, RAND Corporation) examined the impact of benefit design and formulary practices on opioid abuse, overdose, and health system spending in Texas and California. Specific policies examined focused on effects of cost-sharing and the development of a closed formulary.

The third project (PI: Daniel Hartung, Oregon State University) explored how opioid pharmacy benefit polices regarding long-acting opioids and prior authorization for high dosages impact opioid use, abuse, and adverse health outcomes in state Medicaid programs in Oregon, Oklahoma, and Colorado. Results suggest that prior authorization requirements for high dosages can reduce the probability of patients receiving a high dosage prescription and also reduce the use of

multiple pharmacies to obtain opioids (Hartung et al. 2017). Additional results indicate that a prior authorization policy for extended release/long-acting opioids in Oklahoma greatly reduced the number of opioid naïve patients initiating extended release opioids (Keast et al.). Contextual research also found that opioid use and prescribing was highly concentrated among a small group of patients and providers, suggesting that opioid overdose prevention policies should focus efforts on high volume patients and prescribers (Kim et al. 2016).

The fourth project (PI: Gerald Cochran, University of Pittsburgh) assessed how opioid overdoses and misuse differed according to varying formularies and utilization management tools across several health providers contracted as Medicaid providers in Pennsylvania. Underscoring the need for such policies, they found that Pennsylvania Medicaid patients treated for overdose continued to have high opioid prescriptions after the overdose event and only slight increases in the use of medication assisted therapy (Frazier et al. 2017) and that overdoses were more likely among patients with documented opioid use disorder diagnosis as well as among patients with indicators of misuse such as multiple opioid prescribers, multiple pharmacies used, and large number of days supplied (Cochran et al. Medical Care, 2017). Results also suggest that prior authorization formulary policies can reduce opioid misuse and overdoses (Cochran et al. AJMC, 2017).

Research Priority: Evaluate the impact of state policies and strategies that facilitate PDMP use, improve prescribing practices, educate patients, and encourage treatment and overdose response.

Since 2012, the Injury Center has issued three funding opportunity announcements that solicit research to evaluate state policies, including prescription drug monitoring programs (PDMP) and pain clinic legislation. Other policies solicited for evaluation within these announcements focused on formulary management in Medicaid or Worker's Compensation, and cross over with other NCIPC Research Priority areas. Seven projects have been funded in response to two of these announcements (RFA-CE-12-007, RFA-CE-14-002); the other announcement is recent and projects have not yet been awarded (RFA-CE-18-006). Of the seven funded projects, three specifically focused on evaluating Prescription Drug Monitoring Programs.

One project evaluated the health impact of prescription drug monitoring program (PDMP) utilization by prescribers and pharmacists as a means of preventing unintentional prescription drug overdoses in the adolescent and adult population in seven states: New Mexico, Oklahoma, Michigan, North Carolina, Maryland, Missouri, and Tennessee (PI: Green, Rhode Island Hospital). Specifically, it examined laws and regulations governing the use and access of the state PDMPs and actual use of PDMP data by prescribers, pharmacists, and law enforcement personnel. The project also examined the effects of PDMP use on the local demand for opioids, opioid prescribing patterns, and indicators of harm among nonmedical opioid users such as non-oral route of administration, initiation of heroin use, and nonfatal overdose. Results indicated heterogeneity in PDMP policies in regards to overdose-oriented messaging and specific overdose prevention tools made available to providers, suggesting that many state PDMP policies do not clearly communicate their intent to prevent opioid overdoses or provide the tools to facilitate use by providers (Green et al., 2015).

A second project evaluated a PDMP in the context of a novel, multi-component community-based drug overdose prevention program in North Carolina (Project Lazarus) that features community education, provider education, hospital emergency department prescribing policies, diversion control, support programs for pain patients, Naloxone polices, and addiction treatment (PI: Ringwalt, Pacific Institute for Research and Evaluation). Among the components of this program is an effort to increase providers' rates of registry and consultation with the state's PDMP, the Controlled Substances Reporting System (CSRS). Results indicated that provider education related to pain management and addiction treatment, emergency department policies limiting opioid dispensing, and medication assisted treatment for opioid addiction showed beneficial effects in preventing either opioid related emergency department visits or opioid overdose deaths (Alexandridis et al., 2018). In a process evaluation, the investigators discovered that counties with the highest opioid mortality had the highest readiness to respond to the epidemic (Ringwalt et al., 2018). Other research documented early evidence of the shifting of the epidemic from prescription opioids to heroin by assessing trends in North Carolina overdose deaths (Dasguta et al. 2014).

A third project evaluated the effect of PDMP and pain clinic legislation on opioid prescribing behaviors among providers in Florida and Texas (PI: Alexander, Johns Hopkins University). Findings suggested that PDMP and pain clinic legislation can successfully identify high volume opioid prescribing providers and, among these providers, reduce monthly opioid volume and quantity of pills dispensed, average morphine equivalent dose, and number of dispensed opioid prescriptions (Lyapustina et al., 2016, Chang et al., 2016, and Chang et al., 2018).

Research Priority: Identify factors that increase risk for prescription drug-related mortality, and identify risk and protective factors related to the co-use of prescription opioid pain relievers and heroin.

Since 2012, the Injury Center has issued two funding opportunity announcements that solicit research to examine risk factors for prescription drug-related mortality and the co-use of prescription opioids and heroin. Other policies solicited for evaluation within these announcements focused on clinical prescribing guidelines, state policies, including prescription drug monitoring programs (PDMP) and pain clinic legislation, and cross over with other NCIPC Research Priority areas. Five projects have been funded in response to one of these announcements (RFA-CE-16-003), all of which include a focus on risk factors for prescription drug-related mortality and the co-use of prescription opioids and heroin. The other announcement is recent and projects have not yet been awarded (RFA-CE-18-006).

The first project (PI: Peter John Davidson, U of California, San Diego) examines opioid use and misuse and transitions to heroin and injection administration route in three suburban and exurban counties in Southern California. Specifically, the project aims to recruit subjects who misuse prescription opioids or have recently transitioned to heroin or other injection opioid use. A mixed methods approach is being used to investigate initiation of prescription opioids, factors associated with transition to injection opioid or heroin use, and barriers to medication assisted treatment, HIV and Hepatitis testing, overdose prevention and obtaining clean needles.

The second project (PI: Phillip Coffin, PH Foundation Enterprises) examines substance use outcomes among a cohort of 600 patients in the San Francisco Bay Area who were prescribed opioids for chronic pain. Specifically, the study assesses how changes to opioid prescriptions among these patients such as dose reduction or discontinuation (potentially due to new opioid prescribing polices) are associated with initiation of heroin or other injected opioids and overdoses from these drugs.

The third project (PI: Daniel Hartung, Oregon State University) investigates how efforts to reduce opioid doses prescribed across 16 Coordinated Care Organizations serving Oregon Medicaid patients may impact prescribing patterns and the initiation of heroin use and opioid overdoses among patients.

The fourth project (PI: Amy Bohnert, University of Michigan) uses a large national database of medical claims between 2001 and 2015 to examine how individual opioid prescribing patterns relate to later heroin overdoses. A specific focus is to determine if opioid dose reduction or discontinuation are associated with heroin overdoses and to understand patients' contemplation, attitudes towards, and motivation for heroin use after prescription opioids are discontinued or dosage is reduced.

The fifth project (PI: Ingrid Binswanger, Kaiser Foundation Research Institute) assesses the impact of opioid reduction policies such as limits on monthly tablet quantities and average daily dose on adverse outcomes including heroin use and overdose among Medicaid and Kaiser Permanente patients in Colorado.

Research Priority: Evaluate adoption, implementation, and impact of clinical practice guidelines, clinical decision supports, and coordinated care plans within primary care practices in health systems.

Since 2012, the Injury Center has issued five funding opportunity announcements that solicit research to examine clinical practice guidelines, decision supports, and coordinated care plans within primary care practices. Other policies solicited for evaluation within these announcements focused on state policies, including prescription drug monitoring programs (PDMP) and pain clinic legislation, co-use of prescription opioids and heroin, and cross over with other NCIPC Research Priority areas. Ten projects have been funded in response to three of these announcements (RFA-CE-12-007, RFA-CE-14-

004, RFA-CE-16-003), six of which include a focus on clinical practice guidelines, decision supports, and coordinated care plans. The other two announcements are recent and projects have not yet been awarded (RFA-CE-18-004 and RFA-CE-18-006).

The first project evaluates clinical practice guidelines, decision supports, and coordinated care plans in the context of a novel, multi-component community-based drug overdose prevention program in North Carolina that features community education, provider education, hospital emergency department prescribing policies, diversion control, support programs for pain patients, Naloxone polices, and addiction treatment (PI: Ringwalt, Pacific Institute for Research and Evaluation). The provider education component of this program focused on educating medical professionals in chronic pain treatment based upon the North Carolina Medical Board's published guidelines for pain management. Results indicated that this provider education showed beneficial effects in preventing opioid related emergency department visits (Alexandridis et al., 2018). In a process evaluation, the investigators discovered that counties with the highest opioid mortality had the highest readiness to respond to the epidemic (Ringwalt et al., 2018). Other results that provide contextual information to inform clinical guidelines demonstrated large differences in opioid prescribing according to physician specialty (Ringwalt et al. 2014).

The second project examines the use of immediate electronic alerts and feedback to physicians and healthcare providers on potential misuse of prescription opioids by patients (PI: Rachel Seymour, Carolinas Medical Center). The effect of these immediate alerts were examined on outcomes such as physician prescribing behavior, patient behaviors, and rates of outpatient prescription narcotic complications. Process evaluation results published to date have demonstrated that alerts of elevated risk opioid prescriptions can be developed, tested, and tuned sufficiently to ensure a smooth rollout and suggest that buy-in and support from all stakeholders should be obtained early in the process (Seymour et al. 2016).

The third project (PI: Janette Baird, Rhode Island Hospital) evaluates the implementation of a Safe Opioid Prescription Protocol (SOPP) within a level 1 trauma service team. Using chart reviews and interviews, the project assesses opioid use, pain management strategies, and naloxone usage among patients three months after discharge from a care site implementing the SOPP compared to a control site. Further project objectives examine provider behavior regarding opioid prescribing as well as process evaluation of implementing the SOPP protocol. Results demonstrated a high prevalence of potential substance abuse indicators and overdose risk factors among patients in two trauma centers but found no differences in the likelihood of high dose opioid prescriptions based on these characteristics and no evidence of naloxone prescribing (Baird et al. 2017).

The fourth project (PI: Daniel Hartung, Oregon State University) investigates how Performance Improvement Project (PIP) efforts to reduce opioid doses prescribed across 16 Coordinated Care Organizations (CCOs) serving Oregon Medicaid patients can impact prescribing patterns and the initiation of heroin use and opioid overdoses among patients. The project also qualitatively evaluates the policies and procedures developed and implemented by each individual CCOs to meet PIP requirements.

The fifth project (PI: Amy Bohnert, University of Michigan) uses a large national database of medical claims between 2001 and 2015 to examine how individual opioid prescribing patterns relate to later heroin overdoses. A specific focus is to determine if opioid dose reduction or discontinuation, which are often indicted in opioid clinical guidelines, are associated with heroin overdoses. The project also seeks to understand patients' contemplation, attitudes towards, and motivation for heroin use after prescription opioids are discontinued or dosage is reduced.

The sixth project (PI: Ingrid Binswanger, Kaiser Foundation Research Institute) assesses the impact of limits on monthly tablet quantities or average daily dose, which can be features of opioid clinical prescribing guidelines, on adverse outcomes including heroin use and overdose among Medicaid and Kaiser Permanente patients in Colorado.

Injury Control Research Centers (ICRCs) and ICRC Opioid Thematic Network

In 2012 and 2014, the Injury Center also issued funding opportunity announcements to support Injury Control Research Centers (RFA-CE-12-001; RFA-CE-14-001) to conduct research and help translate scientific discoveries into practice for the prevention and control of fatal and nonfatal injuries, violence, and related disabilities. While previous NOFOs have been released to support ICRCs to address NCIPC priorities, only the 2012/2014 announcements/supplements and associated projects were included in this rapid review. Only specific research projects are summarized, without mention of other opioid-related communication, outreach, and training efforts engaged in more broadly by the Centers. Nine projects involving opioid prevention have been undertaken across six prevention research centers. ICRCs are directed to propose research studies that address NCIPC priority areas. The ICRC research projects presented herein address opioid overdose prevention more broadly than the four specific NCIPC Research Priorities (with funding established prior to the publication of the specific NCIPC opioid priorities in 2015), and thus are described separately. This research may be viewed as an important complement to the specific NCIPC priorities to form a more holistic strategy to addressing the epidemic. It is envisioned that future ICRC announcements would point to updated NCIPC research priorities as an anchor point for future work.

Johns Hopkins University's ICRC opioid project (Center PI: Andrea Gielen) aimed to develop and pilot test two mobile device based tools to educate emergency department patients about opioids. The first tool is a patient decision aid completed on a tablet computer in the emergency department prior to the clinician visit. The second tool is a series of tailored education and reminder text messages on safe use, storage, and disposal of prescription opioids for those discharged with a prescription.

North Carolina's ICRC project (Center PI: Stephen Marshall) aims to evaluate the effects of a state Medical Board policy to identify providers who demonstrate potentially excessive opioid prescribing practices based upon PDMP data. The project will determine if identification of high prescribing providers can reduce the number of providers writing prescriptions for high levels of opioids and also examine the impact of the policy on opioid prescriptions for chronic pain patients already on long term opioid treatment at the time of policy implementation.

The Research Institute of Nationwide Children's Hospital's ICRC project (Center PI: Gary Smith) aims to improve the timeliness of opioid overdose surveillance by using national and Ohio state poison control center data to study drug poisonings among adolescents and young adults aged 10-29 years.

University of Iowa's ICRC project (Center PI: Corinne Peek-Asa) uses insurance claim data to examine diagnoses and prescribing patterns associated with opioid abuse, dependence and overdose. It also collects information on county- and regional-level programs and interventions intended to reduce prescription drug abuse and overdose in Iowa.

The University of Michigan ICRC has three opioid related projects (Center PI: Rebecca Cunningham). One project is the further dissemination of an intervention addressing prescription opioid overdose prevention among adults presenting to an emergency department. Another project examines the effect of changes to Medicare coverage for benzodiazepines on the rate of fall-related injuries and unintentional overdoses among individuals age 65+ enrolled in Medicare Advantage plans and for a subset of patients prescribed opioid pain relievers. The third project tests a tailored brief intervention for adults seeking care at an emergency department who were at high risk of unintentional prescription opioid overdose.

The West Virginia University ICRC has two projects addressing opioids (Center PI: Robert Bossarte). The first project examines whether a home visit intervention targeting opioid overdose survivors immediately after the overdose episode can impact overdose recurrence and improve county overdose fatality rate. The second project examines the effect of combining Mindfulness-based Relapse Prevention (MBRP), which has been shown to help with physical and psychological well-being, reduce craving, and help with anxiety and depression, with Medication Assisted Therapy at an opioid dependence treatment center.

NCIPC also funded a thematic network across four of the funded ICRCs to address opioid misuse, abuse, and overdose as a collaborative. The network uses a successful translation model for dissemination and implementation of evidence-based recommendations for addressing the opioid epidemic locally and nationally. Johns Hopkins University, the University of Iowa, the University of Michigan, and West Virginia University were funded to form state-based, expert collaboratives to engage local stakeholders around this issue; update and disseminate a consensus guide that details evidence-based approaches to preventing and addressing opioid misuse, abuse, and overdose; and create and implement a strategic dissemination plan for the guide.

The resulting consensus guide product, "THE OPIOID EPIDEMIC: From Evidence to Impact" synthesized evidence and made recommendations for state level actions to address the opioid epidemic. Key recommendations included CDC research priorities such as Prescription Drug Monitoring Programs, clinical guidelines, and pharmacy benefits manager strategies. Specific state level reports were also prepared for Maryland, Iowa, Michigan, and West Virginia summarizing data and recommending specific actions for each state.

Table 3: Short-term outputs – All funded extramural research projects in the topic area, 2012-2018

RFA	PI	Institution	Amount	Title	Priority
Individual Awards					
CE-12-007	Asheley Skinner	UNC- Chapel Hill	FY12: $197,917 FY13: $198,316	Change in opioid use and overdose after a Medicaid lock-in program	Formulary
CE-12-007	Christopher Ringwalt	Pacific Institute for Research and Evaluation	FY 12: $200,000 FY 13: $197,493	Evaluation of a community-based initiative to prevent opioid overdose	PDMP/Policy, Clinical
CE-12-007	Traci Green	Rhode Island Hospital	FY 12: $198,818 FY 13: $174,303	Local health impacts of prescription drug monitoring program use	PDMP/Policy
CE-14-002	Andrew Mulcahy*	RAND Corporation*	FY 14: $200,000 FY 15: $200,000	The impact of benefit design and formulary practices on opioid abuse and overdose*	Formulary
CE-14-002	Daniel Hartung	Oregon State University	FY 14: $198,806 FY 15: $198,066	Opioid analgesic policies and prescription drug abuse in state Medicaid programs	Formulary
CE-14-002	Gerald Cochran	University of Pittsburgh	FY 14: $199,949 FY 15: $199,946	The influence of formulary management strategies on opioid medication use	Formulary
CE-14-002	Caleb Alexander	Johns Hopkins University	FY 14: $199,984 FY 15: $199,829	The impact of pill mill laws on opioid prescription dispensing and utilization	PDMP/Policy
CE-14-004	Rachel Seymour	Carolinas Medical Center	FY 14: $199,824 FY 15: $199,574	Prescription reporting with immediate medication utilization mapping	Clinical
CE-14-004	Janette Baird	Rhode Island Hospital	FY 14: $199,731 FY 15: $198,003	Safe opioid prescription practice	Clinical
CE-16-003	Peter John Davidson	U of California, San Diego	FY 16: $300,000 FY 17: $300,000	OPR misuse and transitions to heroin and injecting in Southern California	Rx to Illicit
CE-16-003	Phillip Coffin	PH Foundation Enterprises	FY 16: $399,793 FY 17: $399,558	Substance use outcomes of opioid dose reduction and discontinuation	Rx to Illicit
CE-16-003	Daniel Hartung	Oregon State University	FY 16: $398,660 FY 17: $398,660	Prescription opioid performance improvement metrics and heroin abuse	Rx to Illicit Clinical
CE-16-003	Amy Bohnert	University of Michigan	FY 17: $399,823 FY18: TBD	Heroin use and overdose following changes to individual-level opioid prescribing	Rx to Illicit Clinical
CE-16-003	Ingrid Binswanger	Kaiser Foundation Research Institute	FY 17: $399,728 FY18: TBD	Assessing the unintended consequences of restrictive opioid pain reliever policies	Rx to Illicit Clinical
Injury Control Research Center Projects					
CE-14-001	Andrea Gielen	Johns Hopkins University	FY 14: $217,658 FY 15: $221,836 FY 16: $143,287	Using m-Health tools to reduce the misuse of opioid pain relievers	Other

RFA	PI	Institution	Amount	Title	Priority
CE-14-001	Stephen Marshall	University of North Carolina	FY 17: $173,572 FY 18: $178,880	Effects of a state medical board policy identifying providers manifesting potentially excessive opioid prescribing practices	Other
CE-12-001	Gary Smith	Nationwide Children's Hospital	FY 14: $200,000 FY 15: $200,000 FY 16: $100,000	Drug poisonings among adolescents and young adults in Ohio	Other
CE-12-001	Corinne Peek-Asa	University of Iowa	FY 15: $148,999 FY 16: $150,000	Characterization of prescription opioid abuse, dependence, and overdose using insurance claims data from Iowa	Other
CE-12-001	Rebecca Cunningham	University of Michigan	FY 17: $93,329 FY 18: $79,411	Translation of opiate overdose prevention strategies	Other
CE-12-001	Rebecca Cunningham	University of Michigan	FY 18: $38,750	Effect of a prescription drug coverage policy on risk of falls and overdose in older adults	Formulary
CE-12-001	Rebecca Cunningham	University of Michigan	FY 12: $151,277 FY 13: $184,162 FY 14: $102,105	A brief prescription opioid overdose intervention for at-risk urban opioid users	Other
CE-12-001	Robert Bossarte	West Virginia University	FY 17: $169,253 FY 18: $171,502	Home visit after opioid overdose: A project to improve outcomes	Other
CE-12-001	Robert Bossarte	West Virginia University	FY 17: $140,248 FY 18: $69,133	Expanding mindfulness-based relapse prevention in an outpatient setting for patients with opioid use disorders	Other

* Note: This award was supported by an interagency agreement with funds coming to CDC from the National Institute on Drug Abuse, National Institutes of Health.

Figure 2

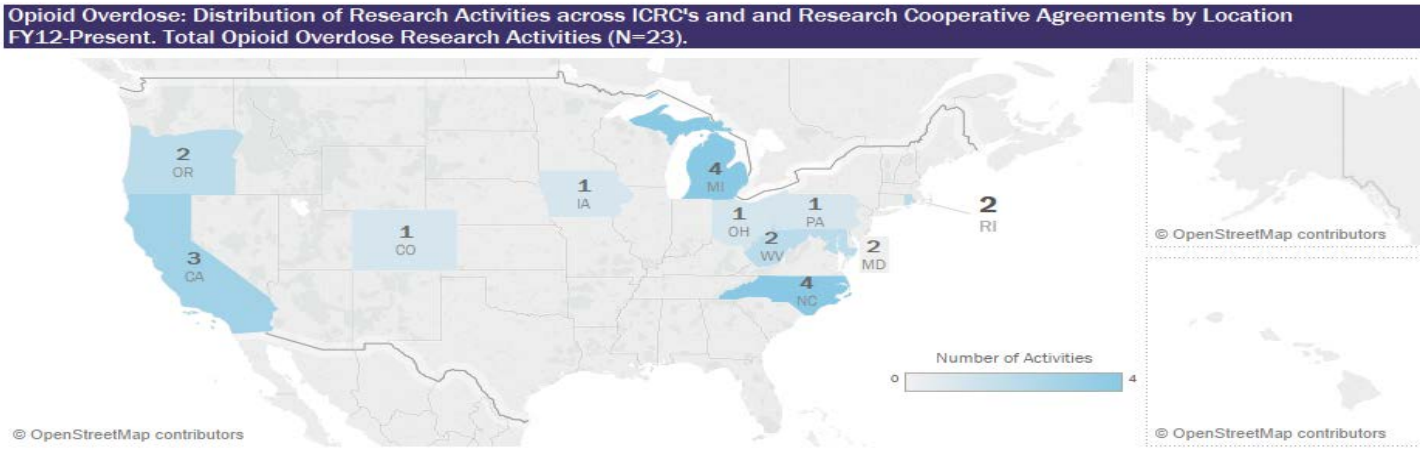


Figure 3

Figure 4

Long-term Outputs

Recently, NCIPC began an initiative to track intramural and extramural research projects and their outputs systematically through a Research Priorities Database. The outputs depicted below (extramural, in particular) are products currently tracked within this database. Note that this list is not comprehensive, and includes products known to the Center and included in the database at the time of this rapid review.

Extramural Research. Table 4 provides a list of publications and products that have emanated from the funded extramural projects. Products are categorized according to the research priority addressed. Figure 5 depicts a sample of key findings addressed by the extramural research. Select findings from the extramural research included in publications presented in Table 4 have also been summarized within the project descriptions included in the short-term outputs section. Table 5 summarizes products that emerged from the ICRC Thematic Research Network.

Table 4: Long-term outputs – Sample of extramural publications and other products for dissemination

Publications	Priority
Chang et al. **Impact of prescription drug monitoring programs and pill mill laws on high-risk opioid prescribers: A comparative interrupted time series analysis**. Drug and Alcohol Dependence 2016;165:1-8.	PDMP/Policy
Skinner et al. **Reducing opioid misuse: Evaluation of a Medicaid controlled substance lock-in program**. The Journal of Pain 2016;17:1150-1155.	Formulary
Naumann et al. **Trajectories of Dispensed Prescription Opioids Among Beneficiaries Enrolled in a Medicaid Controlled Substance "Lock-In" Program**. Pharmacoepidemiology and Drug Safety. 2018: 1-9	Formulary
Cochran et al. **An examination of claims-based predictors of overdose from a large Medicaid program**. Medical Care 2017;55:291-298.	Formulary
Frazier et al. **Medication-Assisted Treatment and Opioid Use Before and After Overdose in Pennsylvania Medicaid.** JAMA. 2017; 318(8): 750-752	Clinical
Roberts et al. **Assessing the present state and potential of Medicaid controlled substance lock-in programs**. Journal of Managed Care Pharmacy 2014;20:439-446.	Formulary
Werth et al. **North Carolina Medicaid recipient management lock-in program: The pharmacist's perspective**. Journal of Managed Care Pharmacy 2014;20:1122-1128.	Formulary
Roberts et al. **Controlled substance lock-in programs: Examining an unintended consequence of a prescription drug abuse policy**. Health Affairs 206;35:1884-1892.	Formulary
Naumann et al. **Evaluating short- and long-term impacts of a Medicaid "lock-in" program on opioid and benzodiazepine prescriptions dispensed to beneficiaries**. Drug and Alcohol Dependence 2018;182:112-119.	Formulary
Alexandridis et al. **A statewide evaluation of seven strategies to reduce opioid overdose in North Carolina**. Injury Prevention 2018;24:48-54.	PDMP/Policy Clinical
Ringwalt et al. **Community readiness to prevent opioid overdose**. Health Promotion Practice 2018; https://doi.org/10.1177/1524839918756887.	PDMP/Policy Clinical
Ringwalt et al. **Differential Prescribing of Opioid Analgesics According to Physician Specialty for Medicaid Patients with Noncancer Pain Diagnoses**. Pain Research and Management 2014; 19(4) 179-185	Clinical
Dasgupta et al. **Observed Transition from Opioid Analgesic Deaths Towards Heroin**. Drug and Alcohol Dependence. Drug and Alcohol Dependence. 2014: (8) 238-241	Rx to Illicit
Green et al. **Discrepancies in addressing overdose prevention through prescription monitoring programs**. Drug and Alcohol Dependence 2015;153:355-358.	PDMP
Baird et al. **A Retrospective Review of Unintentional Opioid Overdose Risk and Mitigating Factors Among Acutely Injured Trauma Patients**. Drug and Alcohol Dependence. 2017. 178: 130-135	PDMP
Yokell et al. **Presentation of prescription and non-prescription opioid overdoses to US emergency departments**. JAMA Internal Medicine 2014;174:2034-2037.	Other
Cochran et al. **Medicaid prior authorization and opioid medication abuse and overdose**. The American Journal of Managed Care 2017;23: 164-171.	Formulary
Hartung et al. **Using prescription monitoring program data to characterize out-of-pocket payments for opioid prescriptions in a state Medicaid program**. Pharmacoepidemiology and Drug Safety 2017;26:1053-1060.	PDMP/Policy
Keast et al. **Effect of a Prior Authorization Policy for Extended-release/Long-Acting Opioids on Utilization and Outcomes in a State Medicaid Program.** Addiction. 2018	Formulary

Publications	Priority
Seymour et al. **Prescription reporting with Immediate Medication Utilization Mapping (PRIMUM): Development of an alert to improve narcotic prescribing**. BMC Medical Informatics and Decision Making 2016;16:111.	Clinical
Kim et al. **The concentration of opioid prescriptions by providers and among patients in the Oregon Medicaid program**. Psychiatric Services 2016;67:397-404.	Formulary
Hartung et al. **Effect of a high dosage opioid prior authorization policy on prescription opioid use, misuse, and overdose outcomes**. Substance Abuse 2017; https://doi.org/10.1080/08897077.2017.1389798.	Formulary
Lyapustina et al. **Effect of a "pill mill" law on opioid prescribing and utilization: The case of Texas**. Drug and Alcohol Dependence 2016;159:190-197.	PDMP/Policy
Chang et al. **Impact of Florida's prescription drug monitoring program and pill mill law on high-risk patients: A comparative interrupted time series analysis**. Pharmacoepidemiology and Drug Safety 2018; https://doi.org/10.1002/pds.4404.	PDMP/Policy
Omaki et al. **Using m-health tools to reduce the misuse of opioid pain relievers**. Injury Prevention 2017; doi:10.1136/injuryprev-2017-042319.	Other
Bohnert et al. **A pilot randomized clinical trial of an intervention to reduce overdose risk behaviors among emergency department patients at risk for prescription opioid overdose**. Drug and alcohol dependence 2016;163:40-47.	Other
Bohnert et al. **Overdose and adverse drug event experiences among adult patients in the emergency department**. Addictive Behaviors 2017; https://doi.org/10.1016/j.addbeh.2017.11.030.	Other
Products	
Clinical decision support alert for opioid prescribing for emergency departments in the electronic health record	Clinical
Mobile app for patient education on prescription opioids	Other
Training and education materials for motivational interviewing and naloxone distribution	Other
Webinars and translation materials	Other
Injury Control Research Center opioid thematic network products	Other

Figure 5: Sample of key findings from extramural research

Formulary Management

In an evaluation of Oregon Medicaid's prior authorization policy for high dose opioids, the probability of an opioid fill over 120 morphine milligram equivalents (MME) declined (a risk factor for overdose), fills of non-opioid medications to treat neuropathic pain increased, and the probability of multiple pharmacy used declined significantly.[1]

PDMP/Policy

In an evaluation of Florida's prescription monitoring program and pill mill law, high risk patients experienced relative reductions in MME, total opioid volume, and number of dispensed opioid prescriptions, while low-risk patients generally did not experience significant relative reductions.[2]

Clinical Care

In an evaluation of Project Lazarus, a state-wide initiative to prevent opioid overdose, provider education and policies to limit emergency department opioid dispensing were associated with lower overdose mortality.[3]

1. Hartung et al. Effect of a high dosage opioid prior authorization policy on prescription opioid use, misuse, and overdose outcomes. Substance Abuse 2017; https://doi.org/10.1080/08897077.2017.1389798.

2. Chang et al. Impact of Florida's prescription drug monitoring program and pill mill law on high-risk patients: A comparative interrupted time series analysis. Pharmacoepidemiology and Drug Safety 2018; https://doi.org/10.1002/pds.4404.

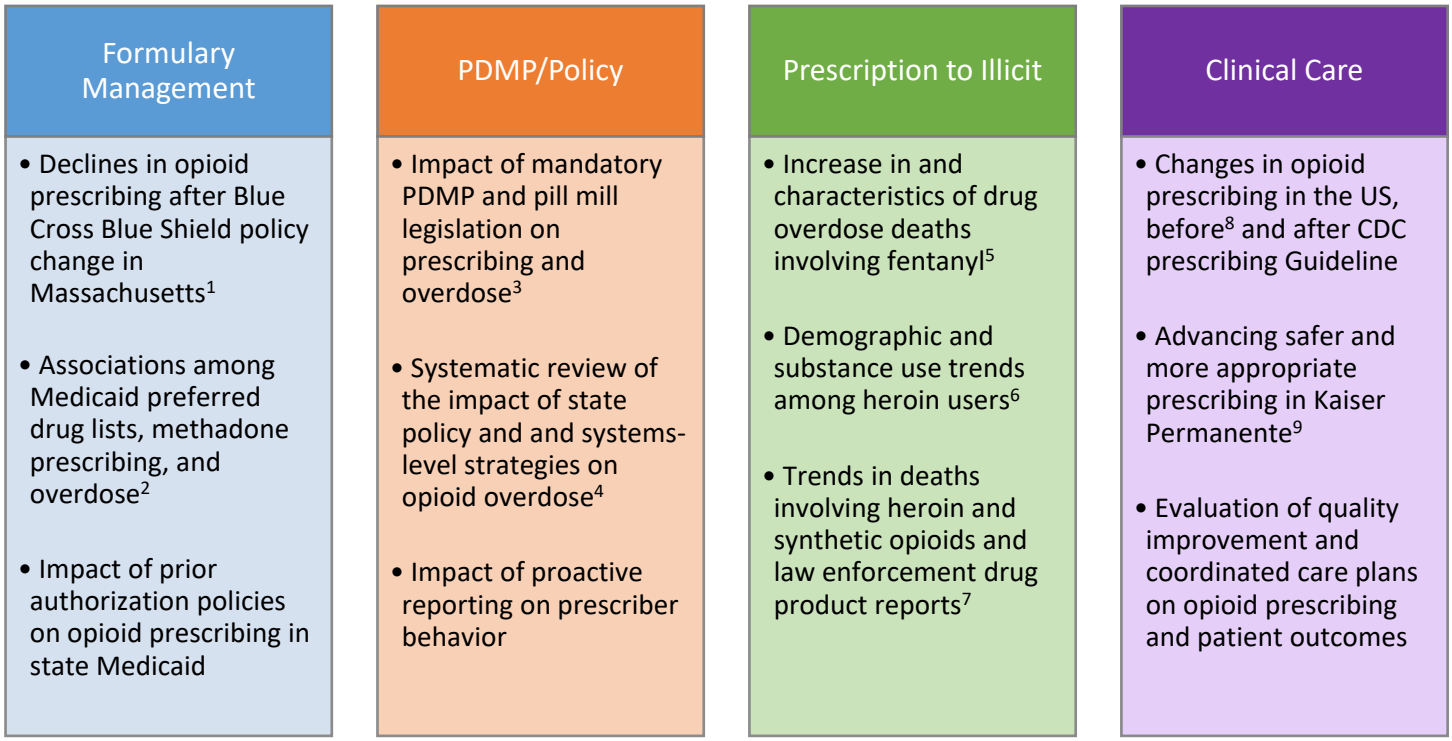
3. Alexandridis et al. A statewide evaluation of seven strategies to reduce opioid overdose in North Carolina. Injury Prevention 2018;24:48-54.

Table 5. Example Injury Control Research Center (ICRC) opioid thematic network products

Injury Control Research Centers	Products
• Johns Hopkins Center for Injury Research and Policy • University of Iowa Injury Prevention Center • University of Michigan Injury Center • West Virginia University Injury Control Research Center	• Actionable guidelines for translating evidence into policy • Strategic dissemination plan for translating research findings into policy • Report on the opioid epidemic for decision makers – from evidence to impact • Policy and program recommendations to reduce opioid overdose and deaths in Iowa • Recommendations for action to prevent opioid deaths in Maryland • An evidence-based approach to the prescription opioid epidemic in Michigan

Intramural Research. A sample of intramural project outputs are summarized in Figure 6 to offer an understanding of how intramural activities serve as an important complement to extramural research. Outputs are categorized by research priority area, and select publications are highlighted for projects that have been completed. This figure represents only a small sample of key work conducted by intramural staff, and is meant to provide a high-level view of critical research activities that inform the priority areas.

Figure 6: Long-term outputs – Sample of intramural projects by research priority



1. Garcia MC, Dodek AB, Kowalski T, Fallon J, Lee SH, Iademarco MF, Auerbach J, Bohm MK. Declines in Opioid Prescribing After a Private Insurer Policy Change — Massachusetts, 2011–2015. MMWR 2016;65:1125-31.
2. Faul M, Bohm M, Alexander C. Methadone prescribing and overdose and the association with Medicaid preferred drug list policies – United States, 2007-2014. MMWR 2017;66:320-323.

3. Dowell D, Zhang K, Noonan RK, Hockenberry JM. Mandatory Provider Review And Pain Clinic Laws Reduce The Amounts Of Opioids Prescribed And Overdose Death Rates. Health Affairs 2016;35:1876-83.
4. Haegerich TM, Paulozzi L, Manns B, Jones CJ. What we know and don't know about the impact of state policy and systems-level strategies on prescription drug overdose. Drug and Alcohol Dependence 2014;145:34-47.
5. O'Donnell JK, Halpin J, Mattson CL, Goldberger BA, Gladden RM. Deaths Involving Fentanyl, Fentanyl Analogs, and U-47700 - 10 States, July-December 2016. Morbidity and Mortality Weekly Report - Early Release. 2017;66:1-6.
6. Jones CM, Logan J, Gladden RM, Bohm MK. Vital Signs: Demographic and substance use trends among heroin users – United States, 2002-2013. MMWR 2015;64:719-725.
7. O'Donnell JK, Gladden RM, Seth P. Trends in Deaths Involving Heroin and Synthetic Opioids Excluding Methadone, and Law Enforcement Drug Product Reports, by Census Region — United States, 2006–2015. MMWR. 2017;66(34):897-903.
8. Guy GP, Zhang K, Bohm MK, Losby J, Lewis B, Young R, Murphy LB, Dowell D. Vital Signs: Changes in opioid prescribing in the United States, 2006-2015. MMWR 2017;66:697-704.
9. Losby JL, Hyatt JD, Kanter MH, Baldwin G, Matuoka D. Safer and more appropriate opioid prescribing: a large healthcare system's comprehensive approach. Journal of Evaluation in Clinical Practice. 2017;1:1-7.

Moving Forward – Setting the context

The epidemic, priorities, and needs for coordination have significantly changed since the research priorities were established. Next, a brief snapshot of how the epidemic has evolved is provided, along with a summary of renewed interest in Center and Agency coordination of efforts to address the epidemic.

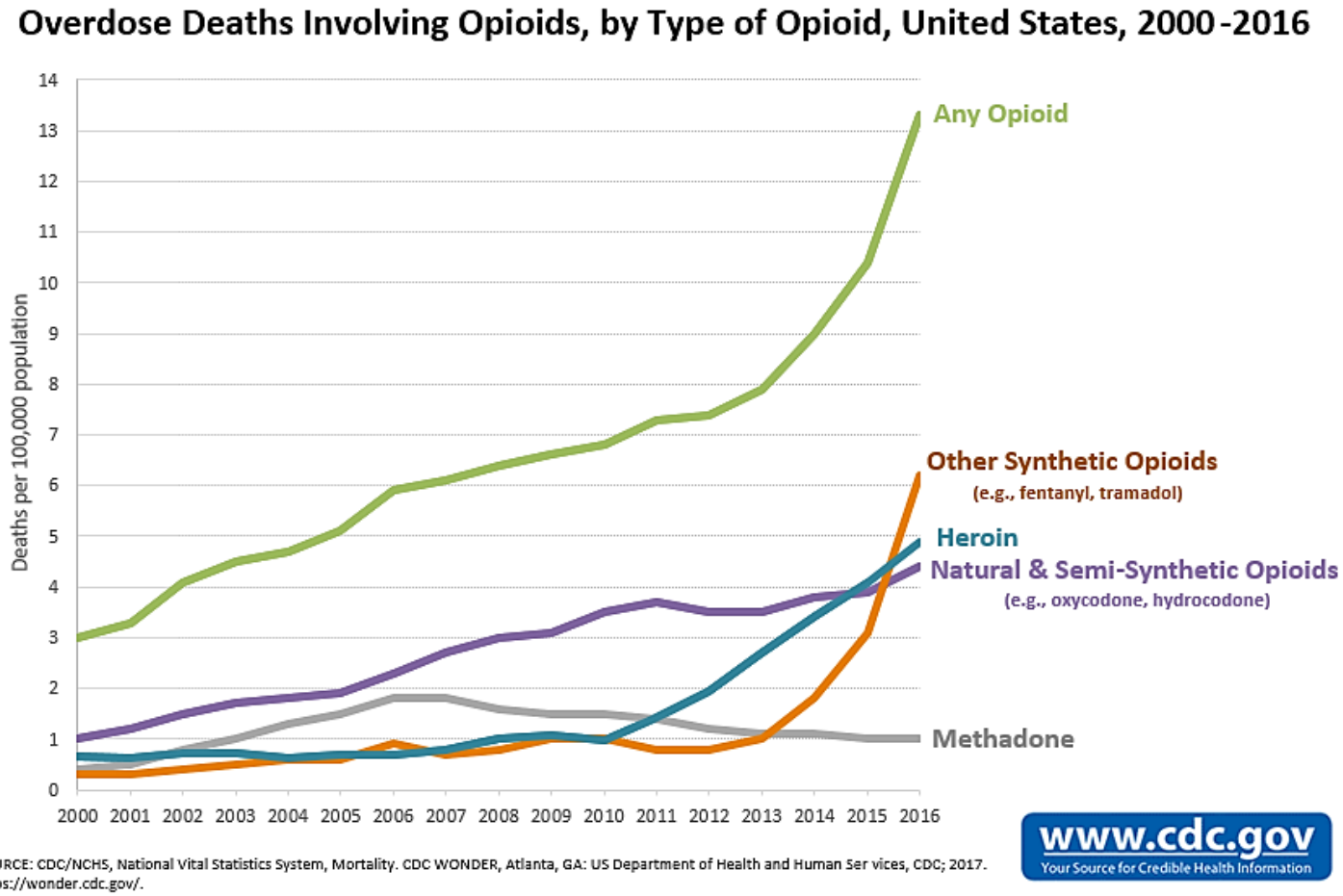
Changes in the Opioid Epidemic

With the evolution of the overdose epidemic shifting from a primary burden associated with prescription opioids to a greater share of the burden from illicit opioids, research priorities may need to shift in response.

Over the past 20 years, the opioid overdose epidemic has evolved in three waves (see Figure 7):

- 1st wave: Increase in deaths involving prescription opioids since 1999
- 2nd wave: Increase in deaths involving heroin since 2010
- 3rd wave: Increase in deaths involving synthetic opioids (illicitly-manufactured fentanyl) since 2013

Figure 7



Shifts in the epidemic have led NCIPC to move toward more comprehensive, coordinated and informed efforts to address opioid overdose and deaths. Table 6 illustrates intramural products that have extended beyond the four research priority areas, illustrating a more comprehensive look at the epidemic through surveillance and research, documenting its evolution (with a sample of publications noted since 2014, given activities that complement the priority areas were being conducted based on the supporting strategic framework).

Table 6: Sample of intramural research products and supportive surveillance products that have extended beyond the four research priority areas

Publications
Vivolo-Kantor AM, Seth P, Gladden RM, Mattson CL, Baldwin GT, Kite-Powell A. **Vital Signs: Trends in emergency department visits for suspected opioid overdoses – United States, July 2016-September 2017**. MMWR 2018;67:279-285.
Guy G, Pasalic E, Zhang K. **Emergency department visits involving opioid overdoses, U.S., 2010-2014.** American Journal of Preventive Medicine 2018;54:e37-39.
Dowell D, Arias E, Kochanek K, Anederson R, Guy Jr GP, Losby JL, Baldwin G. **Contribution of opioid-involved poisoning to the change in life expectancy in the United States, 2000-2015.** JAMA. 2017;318(11):1065-67.
Faul M, Lurie P, Kinsman JM, Dailey MW, Crabaugh C, Sasser SM. **Multiple naloxone administrations among emergency medical service providers is increasing.** Prehospital Emergency Care. 2017;21:1-8.
Jones CM, Christensen A, Gladden RM. **Increases in prescription opioid injection abuse among treatment admissions in the United States, 2004-2013**. Drug Alcohol Dependence. 2017;176:89-95.
Mack K, Jones C, Ballesteros MF. **Illicit drug use, illicit drug use disorders, and drug overdose deaths in metropolitan and nonmetropolitan areas – United States.** MMWR 2017;66:1-12.
Bohnert AS, Logan JE, Ganoczy D, Dowell D. **A detailed exploration into the association of prescribed opioid dosage and overdose deaths among patients with chronic pain.** Medical Care 2016;54(5):435-41.
Dowell D, Haegerich TM, Chou R. **CDC guideline for prescribing opioids for chronic pain -- United States, 2016.** MMWR 2016;65:1-49.
Florence CS, Zhou C, Luo F, Xu L. **The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013**. Medical Care 2016;54:901-906.
Paulozzi L, Zhou C, Jones C, Xu L, Florence C. **Changes in the Medical Management of Patients on Opioid Analgesics Following a Diagnosis of Substance Abuse.** Pharmacoepidemiol Drug Saf. 2016;25(5):545-52.
Van Handel MM, Rose CE, Hallisey EJ, Zibbell JE, Lewis B, Bohm MK, Jones CM, et. al. **County-level vulnerability assessment for rapid dissemination of HIV or HCV infections among persons who inject drugs, United States.** Journal of Acquired Immune Deficiency Syndromes 2016;73(3):323-31.
Zhou C, Florence CS, Dowell D. **Payments for opioids shifted substantially to public and private insurers while consumer spending declined, 1999-2012.** Health Affairs 2016;35(5):824-31.
Paulozzi LJ, Strickler GK, Kreiner PW, Koris CM. **Controlled substance prescribing patterns--Prescription Behavior Surveillance System, Eight states, 2013.** MMWR Surveillance Summaries. 2015;64(9):1-14.
Faul M, Dailey MW, Sugerman DE, Sasser SM, Levy B, Paulozzi LJ. **Disparity in naloxone administration among emergency medical service providers and the burden of drug overdose in rural communities.** American Journal of Public Health 2015;105(Suppl 3):e26-e32.
Mack KA, Zhang K, Paulozzi L, Jones CM. **Prescription practices involving opioid analgesics among Americans with Medicaid, 2010.** Journal of Health Care for the Poor and Underserved 2015;26:182-98.
Baumblatt JA, Wiedeman C, Dunn J, Schaffner W, Paulozzi L, Jones T. **High-risk use by patients prescribed opioids for pain and its role in overdose deaths.** JAMA Internal Medicine 2014;174:796-801.
Johnson H, Paulozzi L, Porucznik C, Mack K, Herter B. **Decline in drug overdose deaths after state policy changes – Florida, 2010-2012.** MMWR 2014;63:1-6.
Jones C, Paulozzi L, Mack K. **Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse–related emergency department visits and drug-related deaths — United States, 2010**. MMWR 2014;63:881-85.
Paulozzi LJ, Mack K, Hockenberry J. **Vital signs: Variation among states in prescribing of opioid pain relievers and benzodiazepines – United States, 2012.** MMWR. 2014;63:1-6.
Rudd RA, Paulozzi LJ, Bauer MJ, et al. **Increases in heroin overdose deaths — 28 States, 2010 to 2012.** MMWR 2014;63:849-54.
Jones C, Paulozzi L, Mack K. **Sources of prescription opioid pain relievers by frequency of past-year nonmedical use: United States, 2008–2011.** JAMA Internal Medicine. 2014;174:802-3.
Paulozzi L, Zhang K, Jones C, Mack K. **Risk of adverse health outcomes with increasing duration and regularity of opioid therapy.** Journal of the American Board of Family Medicine 2014;27:329-38.

Other Current Center Priorities

NCIPC addresses a wide range of injury prevention topics with significant public health burden. Some of the NCIPC priority areas intersect with the opioid overdose epidemic. Building connections between these other priority areas and opioid overdose prevention efforts could enhance public health impact across multiple outcomes. Two topics are of particular intersecting interest: prevention of Adverse Childhood Experiences (ACEs) and suicide.

- **Adverse Childhood Experiences** – ACEs include experiences such as physical, emotional, and sexual abuse; and exposure to household challenges such as intimate partner violence, substance abuse, mental illness, divorce, and family member incarceration. ACEs are linked to risky health behaviors and health outcomes, including opioid misuse. As the number of ACEs increases, so does the risk for negative health outcomes. CDC promotes lifelong health and well-being through *Essentials for Childhood* – assuring safe, stable, and nurturing relationships and environments for all children. ACEs encompass multiple forms of violence. CDC's technical package on preventing child abuse and neglect for policy, norm, and programmatic activities presents key strategies for prevention. Strategies that address the needs of children and their families to prevent ACEs include home visiting to pregnant women and families with newborns, parenting training programs, intimate partner violence prevention, social support for parents, parent support programs for teens and teen pregnancy prevention programs, mental illness and substance abuse treatment, high quality child care, and sufficient income support for lower income families. Many of these strategies prevent other ACEs in adolescence and young adulthood, such as youth violence, teen dating violence, and sexual violence, and may in turn lower the risk for opioid misuse.

  Example intramural research project linking ACEs and opioids

  ACEs have been linked to risky health behaviors, including substance use. In a study in progress, data were drawn from the Behavioral Risk Factor Surveillance System (BRFSS) in two states to test associations between ACE exposure and subsequent prescription opioid misuse in adulthood. Opportunities to prevent opioid misuse start with assuring safe, stable, and nurturing relationships and environments in childhood across the life span. Pain management and opioid prescribing protocols and treatments for opioid use disorder can address ACEs by enhancing safety and effectiveness of clinical care and can reduce the intergenerational continuity of early adversity.

- **Suicide** – Suicide is a serious public health problem that can have lasting harmful effects in on individuals, families, and communities. Suicide rates in the US have increased by nearly 30% between 1999 and 2016, and in 2016 nearly 45,000 lives were lost to suicide. Much is known about the circumstances that contribute to suicide risk, including mental health conditions, substance use, and relationship problems, as well as financial, job, housing, and legal stressors. Suicide can be prevented with the reduction of factors that increase risk and the increase of factors that promote resilience. Broader awareness of increasing suicide rates and effective prevention strategies are needed. CDC's technical package to prevent suicide helps states and communities prioritize strategies with the best available evidence, such as strengthening economic supports, strengthening access and delivery of suicide care, creating protective environments, promoting connectedness, teaching coping and problem-solving skills, identifying and supporting people at risk, lessening harms and preventing future risk. NCIPC has established quarterly meetings of an opioid and suicide interest group to help identify areas of collaboration.

  Example intramural research project linking suicide and opioids

  Suicide risk factors are common among patients with chronic pain, including depression, anxiety, and opioid use. In a study in progress, data from CDC's National Violent Death Reporting System were examined to identify suicide decedents with chronic pain, and the potential contributing factors for suicide and opportunities for prevention. Factors examined included mental health problems (including anxiety disorders), history of suicidal thoughts/plans, and disclosed suicidal intent. Clinicians managing chronic pain can benefit from awareness of suicide warning signs. Diagnosis and management of mental health conditions is an important component of medication management of chronic pain to prevent suicide and promote patient wellbeing.

CDC Opioid Response Coordinating Unit (ORCU)

In 2017, CDC, led by NCIPC, established an intra-agency coordinating unit to assist in priority setting across the agency. The Opioid Research Coordinating Unity (ORCU) articulated CDC's overarching vision and strategy to address opioid overdoses and relate harms, encompassing the relevant work of all Centers, Institutes, and Offices (CIOs), aligned under one set of goals, strategies, actions, and metrics, described in brief below.

Vision: A country free from opioid-related harms and overdose deaths.

Mission: Prevent opioid-related harms and overdose deaths by:

- Using data to monitor emerging trends and direct prevention activities;
- Strengthening state, local, and tribal capacity to respond to the epidemic and prevent opioid-related harms;
- Working with providers, health systems, and payers to reduce unsafe exposure to opioids and treat addiction;
- Coordinating with public safety and community-based partners to rapidly identify overdose threats, reverse overdoses, link people to effective treatment, and reduce harms associated with illicit opioids; and
- Increasing public awareness about the risks of opioids.

Long-term Outcomes:

- Reduce opioid overdose deaths
- Reduce opioid-related morbidity
    - Opioid use disorder
    - Non-fatal overdoses
    - New hepatitis B, hepatitis C, and HIV infections*
    - Maternal and neonatal morbidity including neonatal abstinence syndrome*

Medium-term Outcomes:

- Decrease unsafe prescribing
- Increase use of non-opioid therapies for pain
- Decrease non-medical use of prescription opioids, use of illicit opioids, and use of illicitly-manufactured fentanyl
- Decrease opioid injection and unsafe injection practices*
- Increase use of effective opioid use disorder treatment including medication-assisted therapy
- Increase use of comprehensive prevention services by populations at risk, including testing and treatment of infections related to opioid use and effective treatment for pregnant women with opioid use disorder*
- Increase use of opioid reversing drugs

* *Indicate priorities which are a primary focus area of other CDC centers*

CDC Strategic Framework

CDC Gap Analysis

Research gaps were discussed within ORCU cross-agency deliberations and the following research priorities were identified to address opioid overdose:

- Identify risk and protective factors that influence risk for mortality and inform points for intervention through data linkage, such as with data from PDMPs, hospital discharge, insurance claims, and treatment services.
- Conduct rigorous policy and health system evaluation research to understand the impact of strategies on proximal clinical practice outcomes, as well as distal patient health and economic outcomes.
- Conduct health systems research to identify strategies that increase the use of evidence-based non-opioid treatments such as physical therapy and cognitive behavioral therapy.
- Support identification of quality improvement efforts to facilitate evidence-based decision making at every step of the clinical decision process and improve public health outcomes.
- Conduct systematic reviews of effective policies/programs to inform evidence-based public health interventions.
- Conduct demonstration projects to identify cost-effective methods to reach people using opioids non-medically in hidden populations and engage them in medication-assisted treatment, provision of naloxone and overdose prevention training, prevention, testing, and treatment for infectious and noninfectious sequelae of opioid use.

Key Research Priorities of Other CDC Centers

Other CDC Centers with interests in preventing other opioid-related harms have complementary research priorities. Centers were asked to share their current priorities informally with the ORCU to provide context for NCIPC research agenda setting to ensure work is complementary and not duplicative.

Birth Defects and Developmental Disabilities

- Understand the prevalence of and reasons for opioid use during pregnancy, including the specific opioids and medication combinations used.
- Evaluate the link between prenatal opioid exposure and structural birth defects, including the potential role of co-factors such as infections or other medications.
- Investigate the safety and risk for medications used to treat opioid use disorder for pregnant women and their infants to inform guidelines for treatment.

Reproductive Health

- Identify the barriers for OB-GYNs and Pediatricians to implementing maternal screening for opioid use.
- Identify the factors that influence post-partum relapse for women who enter opioid use disorder treatment during pregnancy.
- Evaluate models of care to improve post-partum counseling and supports for women with a history of opioid use disorder.

HIV/HBV/HCV/STD

- Develop comprehensive community-based approaches to prevent and treat consequences of opioid injection, including substance use disorder, overdose, HIV, hepatitis B and C, and sexually transmitted diseases among key populations including people who inject opioids and other drugs, and young people
- Identify best strategies and develop models for implementing comprehensive community based programs to prevent injection related harms including blood borne pathogens in non-urban settings
- Identify cost-effective methods to reach people using opioids non-medically in hidden populations and engage them in prevention, testing, treatment for the infectious and noninfectious sequelae of opioid use, including early identification of youth at risk for opioid use and ensuring continuity of care and treatment for people after release from the criminal justice system

Occupational Safety and Health

- Identify antecedents to opioid use. For example, how do work and work-related injuries relate to the use of opioids? What kind of prescribing guidelines (e.g., worker's compensation prescribing guidelines) can provide a path to improved health outcomes?
- Understand opioid use at work. For example, how does the use of opioids at work impact worker safety and health? Is employer drug testing an effective strategy for reducing opioid-related work injuries? Do supportive workplace programs improve likelihood of recovery from an opioid drug dependence?
- Address the impacts of misuse and overdose in the workplace. For example, how does opioid misuse and overdose impact first responders? What is the effectiveness of personal protective equipment in protecting first responders? How effective are portable detection devices used by law enforcement to field-test for illicit opioids? What are the psychosocial and mental health impacts of potential exposure to opioids on emergency responders?

Potential new research directions

NCIPC asks for input from the BSC on priorities to be addressed, attending to the identification of a narrow set of priorities. These priorities should be ones that: (1) have the greatest public health impact in the next 3 to 5 years, (2) be supported within the current funding allocation (currently, $5M per year for individual projects, plus additional funds through ICRC allocation), and (3) reduce duplication with other Center, Agency, and Federal efforts.

To assist in obtaining input from the BSC on how research priorities might be expanded to address the evolving epidemic, NCIPC staff engaged in a brief brainstorming session to kick off idea generation. The extensive list of ideas generated in this first session are provided below, and are meant to serve as conversation starters only. Items listed first and marked with an * could be considered as higher priority to address current needs. We generated priorities to address opioid overdose primarily; yet, we also incorporated priorities that address coalescing issues such as suicidal behavior and adverse childhood experiences. Existing priorities have been included and identified as such. Any modifications to research priorities will require feedback from the BSC, further idea generation, discussions, and prioritization, within a comprehensive perspective of NCIPC priorities, funding, and planned activities across the opioid prevention pillars.

Basic epidemiology and etiologic research that identifies best practices for identifying and tracking opioid overdose, as well as the modifiable risk and protective factors associated with opioid overdose

- **IDENTIFICATION**: Identify ways to improve death investigations (e.g., standard protocols), including reporting of intent and precipitating circumstances, toxicology testing, and reporting of overdose on death certificates by medical examiners and coroners*
- **RX VS ILLICIT:** Identify how risk and protective factors and trajectories for opioid misuse, opioid use disorder, and overdose may differ for prescription and illicit opioids, and how prevention strategies may need to be tailored based on unique factors and sub-populations*
- **POPULATIONS**: Identify the populations most at risk for overdose, the unique risk and protective factors associated with those populations, and how prevention strategies may need to be tailored based on population to improve health equity (e.g., homeless, unemployed, older adults, adults with suicidal ideation/behavior, history of ACEs)*
- **DATA LINKAGE**: Identify ways to link data related to opioid overdose from multiple systems, such as PDMPs, electronic health records, public and private insurance claims, and vital statistics, to improve identification and tracking of opioid overdose
- **DESPAIR**: Identify the contribution of individual, family, community, and societal factors associated with "deaths of despair" to opioid overdose
- **BUFFERS/PROTECTIVE FACTORS**: Identify factors at multiple levels of the social ecology that prevent and protect against ACEs to reduce risk for opioid overdose and other health outcomes
- **RX TO ILLICIT (*existing priority*)**: Identify factors that increase risk for prescription-drug related mortality, and identify risk and protective factors related to the co-use of prescription opioid pain relievers and heroin

Effectiveness research that evaluates the impact and cost-effectiveness of programs, practices, and policies on opioid overdose and related outcomes

- **LINKAGES**: Evaluate the effectiveness of programs, practices, and policies that enhance linkage of individuals with opioid use disorder to evidence-based treatment in different contexts and settings (e.g., from primary care, in emergency departments, by law enforcement or emergency medical service providers, through comprehensive syringe services programs, in criminal justice settings) on overdose and other related outcomes such as suicidal behavior and family functioning*
- **PUBLIC SAFETY**: Evaluate programs, practices, and policies that enhance public health and public safety collaborations and connections to respond to overdose and enhance linkage to treatment*

- **UNINTENDED CONSEQUENCES AND BENEFITS**: Evaluate the unintended consequences and benefits of programs, practices, and policies to address opioid overdose (e.g., transition from prescription to illicit misuse, suicidal thoughts and behaviors, child removal as a result of parental help-seeking, improvements in family functioning)*
- **CONTINUUM OF CARE**: Evaluate systems-based approaches across the full continuum from prevention to treatment (e.g., from prescribing to MAT), including approaches that connect multiple stakeholders across communities, for their impact on overdose and related outcomes (e.g., suicidal behavior)
- **RX VS ILLICIT**: Evaluate how the effectiveness of programs, policies, and practices might vary according to type of opioid involved in overdose (e.g., prescription opioid, heroin, illicitly-manufactured fentanyl)
- **NEW OUTCOME**: Evaluate the impact and cost-effectiveness of programs, practices, and policies originally intended to influence other health and social outcomes on opioid overdose (e.g., youth development programs that address common factors underlying violence, adverse childhood experiences, and substance use; community economic development programs)
- **HARM REDUCTION**: Evaluate the effectiveness of harm reduction approaches on opioid overdose, and best practices for formulating such approaches
- **TECHNOLOGY**: Evaluate the best ways to use technology to address opioid overdose and related health outcomes (e.g., clinical decision support in electronic health records, telehealth, other prevention technology)
- **PARTNERS**: Evaluate ways to best engage public health workers as well as new partners across sectors, such as the faith community, in prevention approaches
- **RESPONSE**: Evaluate the effectiveness of response efforts activated when a local opioid-related crisis emerges in a community (e.g., medical response teams activated in response to closing of local pain clinic)
- **UNTESTED STRATEGIES IN THE FIELD**: Evaluate the effectiveness and cost-effectiveness of innovative and established programs, practices, and policies being implemented in states and local communities that have not yet been evaluated
- **VULNERABLE POPULATIONS**: Evaluate innovating prevention strategies designed to address those at greatest risk (e.g., middle-aged adults, those with a history of ACEs, rural and AI/AN populations, incarcerated populations).
- **FORMULARY MANAGEMENT (*existing priority*)**: Evaluate the impact of insurer mechanisms and pharmacy benefit manager strategies to change prescribing behavior, inappropriate use of controlled substances, and patient outcomes [Note: Add – encourage the use of non-opioid therapies]
- **PDMP/STATE POLICY (*existing priority*)**: Evaluate the impact of state policies and strategies that facilitate PDMP use, improve prescribing practices, educate patients, and encourage treatment and overdose response

<u>Dissemination and implementation research</u> that examines the best ways to get science into practice

- **EDUCATION AND TRAINING**: Evaluate effectiveness of different models of healthcare provider training and education, such as online continuing medical education and telehealth approaches (e.g., Project ECHO)*
- **GLOBAL**: Identify approaches used in other countries to disseminate and implement promising practices to address opioid overdose and assess applicability and needed adaptations for the US context*
- **COMMUNITY**: Identify the best methods for scaling up effective community-wide strategies to address opioid overdose, across the full continuum from prevention to treatment, in multiple systems and in different contexts while maintaining effectiveness
- **CLINICAL CARE (*existing priority*):** Evaluate the adoption, implementation, and impact of clinical practice guidelines, clinical decision supports, and coordinated care plans within primary care practices in health systems

<u>Communications research</u> that identifies effective messaging for key audiences, as well as tests the effectiveness of tools and technologies to improve messaging

- **MESSENGERS AND DELIVERY**: Identify the most effective messengers, tools, technologies, and delivery models for disseminating messages to specific audiences*
- **STIGMA**: Identify methods for addressing stigma surrounding opioid use disorder, overdose, disclosure and help-seeking, and naloxone among the public, healthcare providers, public safety professionals, emergency medical service professionals, and others*
- **NORMS**: Identify awareness and norms around overdose and related harms, responsibility, and commitment to prevention, and identify how messaging can best influence norms
- **PUBLIC MESSAGING**: Identify and test the most effective messages for communicating about the risk of prescription and illicit opioids, across different audiences
- **PROVIDER MESSAGING**: Identify and test the most effective messages for communicating about opioid prescribing and pain management to healthcare providers