

National Action Plan for Adverse Drug Event Prevention



U.S. Department of Health and Human Services
Office of Disease Prevention and Health Promotion

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Foreword

I am pleased to share the *National Action Plan for Adverse Drug Event Prevention* (ADE Action Plan). As we know, millions of Americans take medications every day to prevent and treat a variety of health conditions, and advances in therapeutics have improved and saved millions of lives. However, medications can also cause harms—known as adverse drug events (ADEs)—that are often preventable. ADE prevention is an important patient safety priority, with ADEs accounting for an estimated one-third of hospital adverse events and approximately 280,000 hospital admissions annually. The Department of Health and Human Services (HHS) encourages the prevention of adverse drug events through coordination and partnerships with public and private sector stakeholders.

The ADE Action Plan identifies efforts to date to measure and prevent ADEs, and promote medication safety. In addition, this plan outlines future opportunities to advance patient safety with regard to the prevention of adverse drug events among three primary drug classes: anticoagulants, diabetes agents, and opioids. The ADE Action Plan is intended to encourage nationwide efforts to coordinate Federal resources and activities that will reduce preventable adverse drug events and increase awareness of the importance of medication safety.

Achieving high-quality health care for all Americans is a top priority for the U.S. Government. By improving patient safety, we can lower health care costs for the Nation and improve the care that we provide to patients, their families, and the community at large. Through ongoing collaboration, we can realize our vision of a healthy and productive society. Patients across the nation depend on our efforts to ensure that the health care they receive is effective and efficient, and guarantees the highest quality of care.

The ADE Action Plan helps achieve the Nation’s goal to strengthen health systems by improving the quality of health care and ensuring patient safety. Through ongoing efforts and the investment of resources to prevent unnecessary medication errors and resulting complications, America can become a stronger and healthier Nation. The *National Action Plan for Adverse Drug Event Prevention* is a major step toward realizing this vision.

Sincerely,

Howard Koh, M.D., M.P.H.
Assistant Secretary for Health
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List of Acronyms

Federal Agencies

ACL	Administration for Community Living
AHRQ	Agency for Healthcare Research and Quality
ASPE	Assistant Secretary for Planning and Evaluation
BOP	Bureau of Prisons
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare & Medicaid Services
DEA	Drug Enforcement Administration
DOD	Department of Defense
FDA	Food and Drug Administration
HHS	U.S. Department of Health and Human Services
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
NIH	National Institutes of Health
OASH	Office of the Assistant Secretary for Health
ODPHP	Office of Disease Prevention and Health Promotion
OIG	Office of the Inspector General
ONC	Office of the National Coordinator for Health Information Technology
SAMHSA	Substance Abuse and Mental Health Services Administration
VA	Department of Veterans Affairs

Acronyms

AACE	American Association of Clinical Endocrinologists
ACA	Affordable Care Act
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACCP	American College of Chest Physicians
ACO	Accountable Care Organization
ACP	American College of Physicians
ADA	American Diabetes Association
ADE	adverse drug event
ADR	adverse drug reaction
ADVANCE	Action in Diabetes and Vascular Disease
AF	atrial fibrillation
AGS	American Geriatrics Society

AMDA	American Medical Directors Association
AO	National Accreditation Organization
APhA	American Pharmacists Association
aPTT	activated partial thromboplastin time
BG	blood glucose
BMI	body mass index
CAH	critical access hospital
CCTP	Community-Based Care Transitions Program
CDS	clinical decision support
CE	continuing education
CfC	Condition for Coverage
CHF	congestive heart failure
CHIP	Children’s Health Insurance Program
CLAS	National Culturally and Linguistically Appropriate Services
CME	continuing medical education
CMMI	Center for Medicare & Medicaid Innovation
CMO	chief medical officer
CoP	Condition of Participation
CPOE	computerized physician/provider order entry
CPT	Current Procedural Terminology
DAWN	Drug Abuse Warning Network
DCCT	Diabetes Control and Complications Trial
DM	diabetes mellitus
DSME	diabetes self-management education
DUE	drug use evaluation
DUR	drug utilization review
DVT	deep vein thrombosis
E/M	evaluation and management
E-codes	external causes of injury codes
ED	emergency department
EH	eligible hospital
EHR	electronic health record
EP	eligible professional
e-prescribing	electronic prescribing
FAERS	Food and Drug Administration Adverse Event Reporting System
FIW	Federal Interagency Workgroup
HAI	health care-associated infection
HAS-BLED	Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol Concomitantly
HbA1c	hemoglobin A1c
HCUP	Healthcare Cost and Utilization Project
HEN	hospital engagement network
health IT	health information technology
HITECH	Health Information Technology for Economic and Clinical Health

HVBP	Hospital Value-Based Purchasing
ICD	International Classification of Diseases
ICPCA	Integrating Care for Populations and Communities Aim
ICU	intensive care unit
IHI	Institute for Healthcare Improvement
IIT	intensive insulin therapy
INR	international normalized ratio
IQR	inpatient quality reporting
ISMP	Institute for Safe Medication Practices
iTTR	individual time in therapeutic range
IV	intravenous
LMWH	low-molecular-weight heparin
LTC	long-term care
LTCF	long-term care facility
MAPCP	Multi-Payer Advanced Primary Care Practice
MCBS	Medicare Current Beneficiary Survey
MED	morphine equivalent dose
mg/dL	milligrams per deciliter
MI	myocardial infarction
MMCO	Medicare-Medicaid Coordination Office
mmol	millimoles
MPSMS	Medicare Patient Safety Monitoring System
MR	modified release (tablets)
mTBI	mild traumatic brain injury
MUET	medication use evaluation template
NASCOLA	North American Specialized Coagulation Laboratory Association
NCD	national coverage determination
NCHS	National Center for Health Statistics
NDEP	National Diabetes Education Program
NEDS	Nationwide Emergency Department Sample
NEISS-CADES	National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance
NGSP	National Glycohemoglobin Standardization Program
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHSN	National Healthcare Safety Network
NICE-SUGAR	Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation
NIS	Nationwide Inpatient Sample
NOAC	new oral anticoagulant
NPSG	National Patient Safety Goal
NPV	negative predictive value
NQF	National Quality Forum
NVSS	National Vital Statistics System
PBSS	Prescription Behavior Surveillance System

PC-PTSD	Primary Care-Posttraumatic Stress Disorder Screen
PDMP	Prescription Drug Monitoring Program
PE	pulmonary embolism
PHQ-2	Patient Health Questionnaire
POC	point-of-care
PPV	positive predictive value
PQI	Prevention Quality Indicator
PQRS	Physician Quality Reporting System
Project RED	Project Re-Engineered Discharge
PSI	Patient Safety Indicator
PSM	patient self-monitoring
PSPC	Patient Safety and Clinical Pharmacy Collaborative
PST	patient self-testing
PT	prothrombin time
QIO	Quality Improvement Organization
REMS	Risk Evaluation and Mitigation Strategy
RPMS-EHR	Resource and Patient Management System-Electronic Health Record
S&C	survey and certification
SA	State Survey Agency
SES	socioeconomic status
SPP	Sole Provider Program
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TJC	The Joint Commission
TMS	Talent Management System
TTR	time in therapeutic range
UFH	unfractionated heparin
VA ADERS	Department of Veterans Affairs (VA) Adverse Drug Event Reporting System
VADT	Veterans Affairs (VA) Diabetes Trial
VBP	Value-Based Purchasing
VKAs	vitamin K antagonists
VTE	venous thromboembolism

Executive Summary

The *National Action Plan for Adverse Drug Event Prevention* (ADE Action Plan) was established to address two key objectives: (1) identify common, preventable, and measurable adverse drug events (ADEs) that may result in significant patient harm; and (2) align the efforts of Federal health agencies to reduce patient harms from these specific ADEs nationally.

On the basis of national ADE data from inpatient and outpatient settings, three types of ADEs were considered to be common, clinically significant, preventable, and measurable, and were therefore selected as the high-priority targets of the ADE Action Plan.

The three initial targets of the ADE Action Plan are

- Anticoagulants (primary ADE of concern: bleeding)
- Diabetes agents (primary ADE of concern: hypoglycemia)
- Opioids (primary ADE of concern: accidental overdoses/oversedation /respiratory depression)

The ADE Action Plan suggests a four-pronged approach to reduce patient harms from these three ADEs: **Surveillance, Prevention, Incentives and Oversight, and Research.**

- 1) **Surveillance**—Coordinate existing Federal **surveillance** resources and data to assess the health burden and rates of ADEs.

Federal public health agencies will strive to coordinate ADE surveillance efforts to assess progress in the prevention of anticoagulant, diabetes agent, and opioid ADEs at a population-based level. Federal Agencies that provide direct patient care¹ will identify opportunities for assessing progress in preventing anticoagulant, diabetes agent, and opioid ADEs within their health care delivery networks. Using enhanced and more consistent definitions of ADEs,

¹ These agencies include but are not limited to the Bureau of Prisons, Department of Defense, Health Resources and Services Administration, Indian Health Service, and Veterans Health Administration.

specifically those associated with high-priority ADE targets (i.e., anticoagulants, diabetes agents, opioids), can allow for more effective measuring and tracking of ADEs.

- 2) **Prevention**—Share existing **evidence-based prevention tools** across Federal Agencies and with non-Federal health care providers and patients.

Federal public health agencies that support the development and dissemination of evidence-based prevention tools will promote the dissemination of these tools to prevent anticoagulant, diabetes agent, and opioid ADEs, and will collaborate with Federal Agencies that provide direct patient care to disseminate the evidence-based prevention tools these agencies use, particularly for high-risk patient populations (e.g., older adults and people with disabilities) and for high-risk situations and settings in which ADE prevention strategies may be lacking (e.g., care transitions, institutional and noninstitutional long-term care).

- 3) **Incentives and Oversight**—Explore opportunities, including financial **incentives and oversight** authorities, to promote ADE prevention.

Federal public health agencies and agencies that provide direct patient care share a commitment to improving patient safety and will explore opportunities to incorporate the prevention of anticoagulant, diabetes agent, and opioid ADEs within existing safety and quality programs, measures, and payment models.

- 4) **Research**—Identify current knowledge gaps and future **research needs (unanswered questions)** for ADE prevention.

Federal health agencies will collaborate to identify key research needs and facilitate the basic, translational, and health services research required to identify the most effective strategies for the prevention of anticoagulant, diabetes agent, and opioid ADEs, particularly among high-risk patients.

Within each of the sections dedicated to the three high-priority targets for ADE prevention efforts, figures highlight the most pertinent actions to potentially advance the areas of surveillance, evidence-based prevention tools, incentives and oversight, and research, as well as the role of health information technology.

The Department of Health and Human Services (HHS) is releasing the final *National Action Plan for Adverse Drug Event Prevention*, following issuance of a draft ADE Action Plan and review of public

comments. The success of the ADE Action Plan will depend on ongoing coordination and collaboration across the Federal Government and among Government Agencies, national experts, and key public and private stakeholders. The ADE Action Plan should serve as a catalyst for leaders at the Federal, State, and local levels to implement evidence-based guidelines and engage in strategies that will help advance the goals of the ADE Action Plan. As progress is made toward reducing ADEs from the initial targets of the ADE Action Plan (i.e., anticoagulants, diabetes agents, and opioids), prevention efforts will need to be retooled to include additional and newly emerging medication safety targets.

Introduction

This *National Action Plan for Adverse Drug Event Prevention* (ADE Action Plan) seeks to engage all stakeholders in a coordinated, aligned, multisector, and health-literate effort to reduce the ADEs that are most common, clinically significant, preventable, and measurable. The ADE Action Plan identifies the Federal Government’s highest priority strategies and opportunities for advancement, which will have the greatest impact on reducing ADEs. Implementation of these strategies is expected to result in safer and higher quality health care services, reduced health care costs, informed and engaged consumers, and ultimately, improved health outcomes.

The Office of Disease Prevention and Health Promotion (ODPHP), in conjunction with the Federal Interagency Steering Committee and Workgroups for ADEs, led the development of the ADE Action Plan. Specifically, representatives of as many as 13 Federal Agencies and non-Federal subject matter expert consultants contributed to the ADE Action Plan, to draw attention to ADEs as a major patient safety and public health issue.

The ADE Action Plan provides Federal Agencies and external stakeholders with a framework to identify strategies and select specific actions to take. The intended end users of the Action Plan are policymakers, health care professionals, public and private sector organizations, and communities that can organize and take action toward preventing high-priority ADEs.

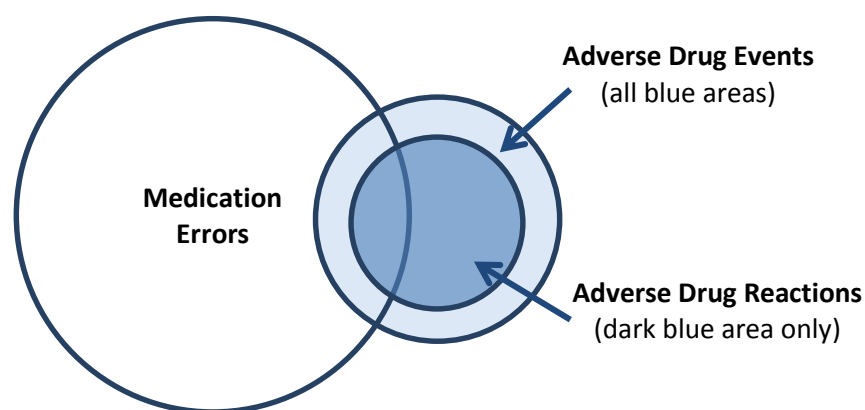
The ADE Action Plan is organized into seven sections. The first four sections outline the scope and development of the ADE Action Plan, identify Federal surveillance resources to measure and monitor the burden of ADEs, describe overall prevention approaches by identifying key determinants of ADEs, and review incentives and oversight opportunities to prevent ADEs. The next three sections of the ADE Action Plan address in detail the high-priority ADE targets (anticoagulants, diabetes agents, and opioids) that are the focus of the ADE Action Plan, highlighting the most pertinent actions to potentially advance each of the areas of surveillance, evidence-based prevention tools, incentives and oversight, and research (unanswered questions), as well as the role of health information technology (health IT) in advancing these efforts. Some of these sections provide recommendations or information that informs other areas. The final section presents conclusions and outlines next steps.

Adverse Drug Events: Magnitude of the Problem

ADE Prevention Is a Patient Safety Priority

An adverse drug event has been defined by the Institute of Medicine as “an injury resulting from medical intervention related to a drug” [1]. This broad term encompasses harms that occur during medical care that are directly caused by the drug including but are not limited to medication errors, adverse drug reactions, allergic reactions, and overdoses [1] [Figure 1]. A medication error is defined as “inappropriate use of a drug that may or may not result in harm;” such errors may occur during prescribing, transcribing, dispensing, administering, adherence, or monitoring of a drug [2,3]. In contrast, an adverse drug reaction (ADR) is “harms directly caused by a drug at normal doses” [3].

Figure 1. Terms Relevant to Drug-Related Harm [2]



A large majority of ADEs are preventable. In 2006, 82 percent of the United States population reported using at least one prescription medication, over-the-counter medication, or dietary supplement, and 29 percent reported using five or more prescription medications [4]. Among older adults (65 years of age or older), 57–59 percent reported taking five to nine medications and 17–19 percent reported taking 10 or more over the course of that year [4]. Given the U.S. population’s large and ever-increasing magnitude of medication exposure, the potential for harms from ADEs constitutes a critical patient safety and public health challenge.

ADEs can occur in any health care setting, including inpatient (e.g., acute care hospitals), outpatient, and institutional and noninstitutional long-term care (LTC) settings (e.g., nursing homes, group homes). The likelihood of ADEs occurring may also increase during transitions of care (e.g., discharge from a hospital to a nursing home or patients’ move from one health care provider or setting to another), when

information may not be adequately transferred between health care providers [5] or patients may not completely understand how to manage their medications [6, 7, 8].

In inpatient settings, research indicates that ADEs are among the largest contributors to hospital-related complications [9, 10]. It has been estimated that ADEs comprise one-third of hospital adverse events [9], affect approximately 2 million hospital stays annually [9, 11], and prolong hospital length of stay by approximately 1.7 to 4.6 days [11, 12, 13]. Data regarding how ADEs contribute to postdischarge complications or during other types of care transitions are lacking. One single-center study based in a tertiary care academic medical center identified ADEs as the most common cause of postdischarge complications occurring within 3 weeks of hospital discharge (accounting for two-thirds of postdischarge complications) [14]; in this study, 24 percent of postdischarge ADEs were judged to be preventable, and in another, similar study, 27 percent of postdischarge ADEs were judged to be preventable and 33 percent ameliorable [15]. In outpatient settings, nationally representative surveillance data indicate that ADEs account for more than 3.5 million physician office visits [16], an estimated 1 million emergency department (ED) visits [17], and approximately 125,000 hospital admissions each year [17]. An analysis of 2011 data indicated that ADEs were three times more likely to be present on admission than during the hospital stay [18].

The economic impact of ADEs has been inadequately studied. Older data indicate that ADEs impose a large financial burden on health care expenditures [12, 13]; one study estimated ADEs incurred \$5.6 million (1993 USD) in excess hospital costs [12]. National estimates suggest that ADEs contribute an additional \$3.5 billion (2006 USD) to U.S. health care costs [19]. Older adults experience the highest population rates of ADEs resulting in ED visits and are seven times more likely than younger persons to have an ADE that requires emergent hospital admission [16, 20]. Analysis of 2011 data indicated that Medicare beneficiaries are at the highest risk of acquiring an ADE during a hospital stay with Medicare reimbursing 75 percent of inpatient ADEs attributable to the most common medications [20]. These ED visits and hospital admissions from ADEs, a significant number of which are considered preventable, contribute to an enormously overburdened Medicare system [9].

Focus on High-Impact Targets and Populations

The *National Action Plan for Adverse Drug Event Prevention* focuses on common, clinically significant, preventable, and measurable ADEs. A key group of ADEs are particularly dangerous and largely preventable, and for these reasons, they are high-priority targets for national and local ADE prevention efforts.

Medication Classes Most Commonly Implicated in ADEs

In a nationally representative sample of hospitalized Medicare beneficiaries, the targets of the ADE Action Plan were identified as three of the most commonly implicated drug classes in ADEs: *anticoagulants*, *opioids*, and *insulin* [9]. Conservative estimates indicate that hospitalized patients experience 380,000 to 450,000 ADEs each year, with a large majority of these attributable to anticoagulants and opioids [17]. A large percentage of these ADEs were judged to be preventable.

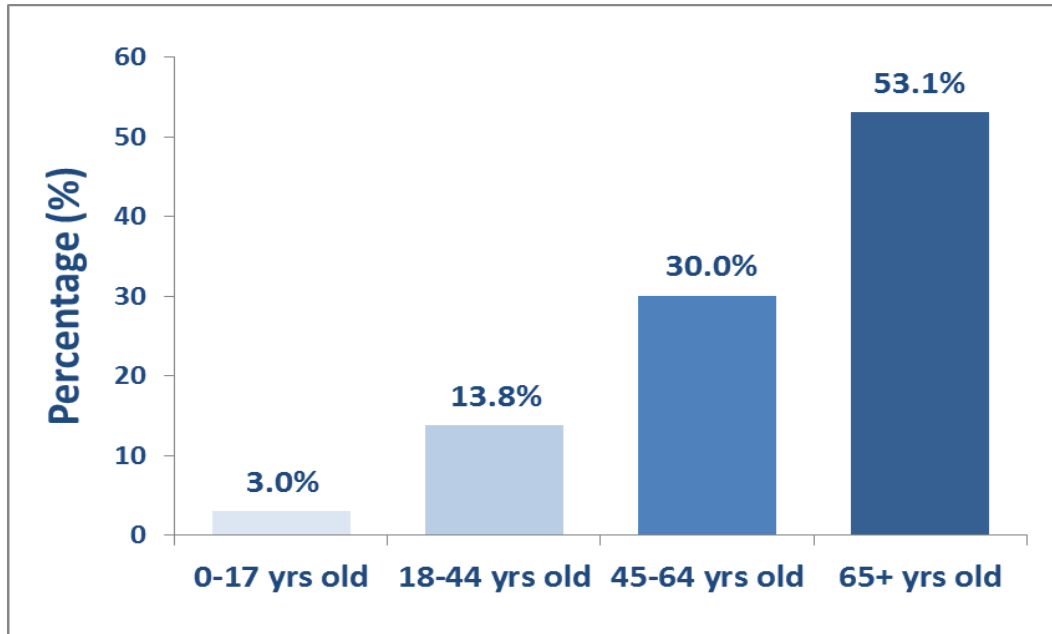
In outpatient settings, national public health surveillance data indicate that a small group of key medication classes—those that are characterized by a narrow therapeutic index or require routine laboratory monitoring—cause the most outpatient medication-related harms [19, 21]. In a recent, nationally representative sample of hospital admissions for ADEs among older adults, an estimated two-thirds of admissions involved just four medication classes, three of which are preventable targets of the ADE Action Plan: *anticoagulants* (e.g., warfarin), *insulin*, and *oral diabetes agents* (e.g., sulfonylurea) [20]. A significant proportion of ADEs in this sample resulted from unintentional overdoses or suprathreshold effects (e.g., bleeding due to excessive anticoagulation or hypoglycemia from excessive insulin administration) [20].

Most Vulnerable Populations

It is recognized that several patient populations may be especially vulnerable to ADEs, including the very young (pediatric patients), older adults, individuals with low socioeconomic status (SES) or low health literacy, those with limited access to health care services, and certain minority races or ethnic groups. To date, data commonly implicate age as a principle underlying risk factor for ADEs and suggest that older adults are particularly vulnerable to ADEs, likely owing to altered pharmacokinetics, polypharmacy, or cognitive decline [22, 23, 24]. For example, older adults comprise approximately 35 percent of all inpatient stays but contribute to approximately 53 percent of inpatient stays complicated by ADEs [Figure 2] [11]. Analyses of cost data indicate that Medicare-covered patients experience significantly higher rates of ADEs than both privately insured and Medicaid-covered patients. In the outpatient setting, national surveillance data indicate that older adults are two to three times more likely to have an ADE requiring a physician office or ED visit and seven times more likely to have an ADE requiring hospital admission [Figure 3] [19, 20]. The aging of the population and the vulnerability of older adults to ADEs will have significant implications for Medicare. In 2050, the number of Americans aged 65 and older is projected to be 88.5 million, more than double its population in 2010 of 40.2 million [25]. Spending in the United States for prescription drugs in 2010 was \$259.1 billion and is expected to double

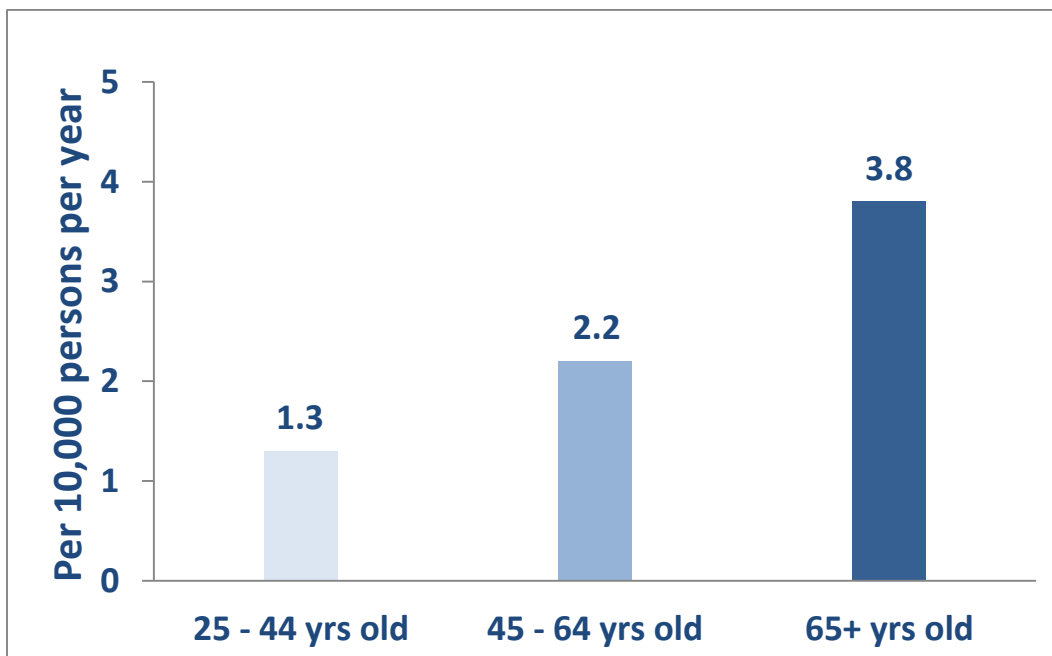
over the next decade [26]. Total expenditures on the Medicare Part D program alone in 2012 were \$66.9 billion and are projected to reach \$165.1 billion by 2022 [27].

Figure 2. Hospital Stays Complicated by Adverse Drug Events, Distribution by Age [11]*



*2008 data analyzed from the Healthcare Cost and Utilization Project, AHRQ

Figure 3. Rate of Ambulatory Visits for Adverse Drug Events, Distribution by Age [28]*



*2005–2007 data analyzed from the National Ambulatory Medical Care Survey and the National Hospital and Ambulatory Medical Care Survey, CDC

Underserved and Rural Communities

Any steps to reduce the incidence of ADEs should take into consideration the available resources of the health care provider, institution, and surrounding community. In underserved and rural communities, limited access to health care services, shortages of qualified health care personnel, slower adoption of electronic health records (EHRs), higher rates of older adults with chronic conditions, low health literacy, and reduced revenue may affect the successful implementation of approaches outlined in this document [29, 30].

Limited staff resources and slower adoption of EHRs affect current surveillance efforts, which rely on clinical chart abstractions. In a rural or underserved community, the health care provider may be forced to choose between dedicating time to patient care and investing time in reporting rates of ADEs. Even as the Nation moves toward a more seamless system for reporting these errors through the use of EHRs, underserved communities will be at a disadvantage, as EHR adoption rates continue to be higher within facilities with more financial resources, and rural communities continue to lag behind their urban counterparts [31, 32].

Implementing ADE prevention efforts requires extensive staff training, investment of financial resources, and coordination of providers—all of which may be challenging in communities where staffing is limited, providers are not located within the same geographic community, and financial resources are scarce [33]. In rural communities especially, coordination of medications across health care providers may be limited, as only generalists may be available in the community and prescribing specialists may be many miles away [34]. Rural and underserved communities may be less capable of taking advantage of advances in technology, such as the use of clinical decision support (CDS) in EHRs, and are less likely to have access to e-prescribing systems, which serve as a valuable tool to track inappropriate dosages, drug-drug interactions, and drug-allergy interactions.

The complexity of the care that pharmacists provide patients necessitates that patients should have access to the health care provider responsible for their care during all aspects of medication therapy. Although such local access is not always possible in low-volume, rural settings, leveraging technology to access remotely delivered care can result in both direct intervention and enhanced patient education. Provider involvement is crucial to supporting consumer engagement in shared decisionmaking regarding medication management. This may be more challenging within underserved and rural communities, as evidence suggests that individuals in rural communities and those with lower SES have lower health literacy [29].

Rural health care providers like critical access hospitals (CAHs) are not subject to some of the same reporting requirements and financial incentive programs as other providers. For example, although the majority of CAHs report quality measure information to the Centers for Medicare & Medicaid Services' (CMS) Hospital Compare Web site, these hospitals are exempt from this requirement, which means that changes in CMS programs and policies may not have the same impact on some rural populations.

Finally, within underserved communities, there is a significant delay in the translation of research into practice [35]. Thus, even proven interventions or new findings related to reducing ADEs may take many years to benefit rural and underserved communities.

Federal Interagency Steering Committee and Workgroups for ADEs

The Call for Action

In 2010, the President signed the Patient Protection and Affordable Care Act (Affordable Care Act) into law, strengthening and modernizing health care [36]. One of the goals of the Affordable Care Act is to reduce the mounting health care costs that have put a strain on patients, employers, and our Federal budget. The U.S. Department of Health and Human Services (HHS) is responsible for implementing many of the health reform changes, including an objective aimed at improving health care quality and ensuring patient safety. In order to achieve this objective, HHS has developed several key strategies, two of which relate directly to ADEs:

- Reduce health care–associated infections, ADEs, and other complications of health care delivery through quality and safety promotion efforts.
- Establish the Partnership for Patients, a public–private partnership to help improve the quality, safety, and affordability of health care for all Americans.

In December 2011, the U.S. Senate sent a bipartisan letter to the Secretary of HHS requesting that the Department convene a Federal interagency task force to identify patients at risk for ADEs and opportunities to improve the care provided to patients at highest risk for ADEs. The letter specifically requested that the task force include in their considerations care transitions, the role of health IT, identification of existing and needed measures, and the impact of new Medicare reimbursement models. The ADE Action Plan specifically addresses each of these considerations.

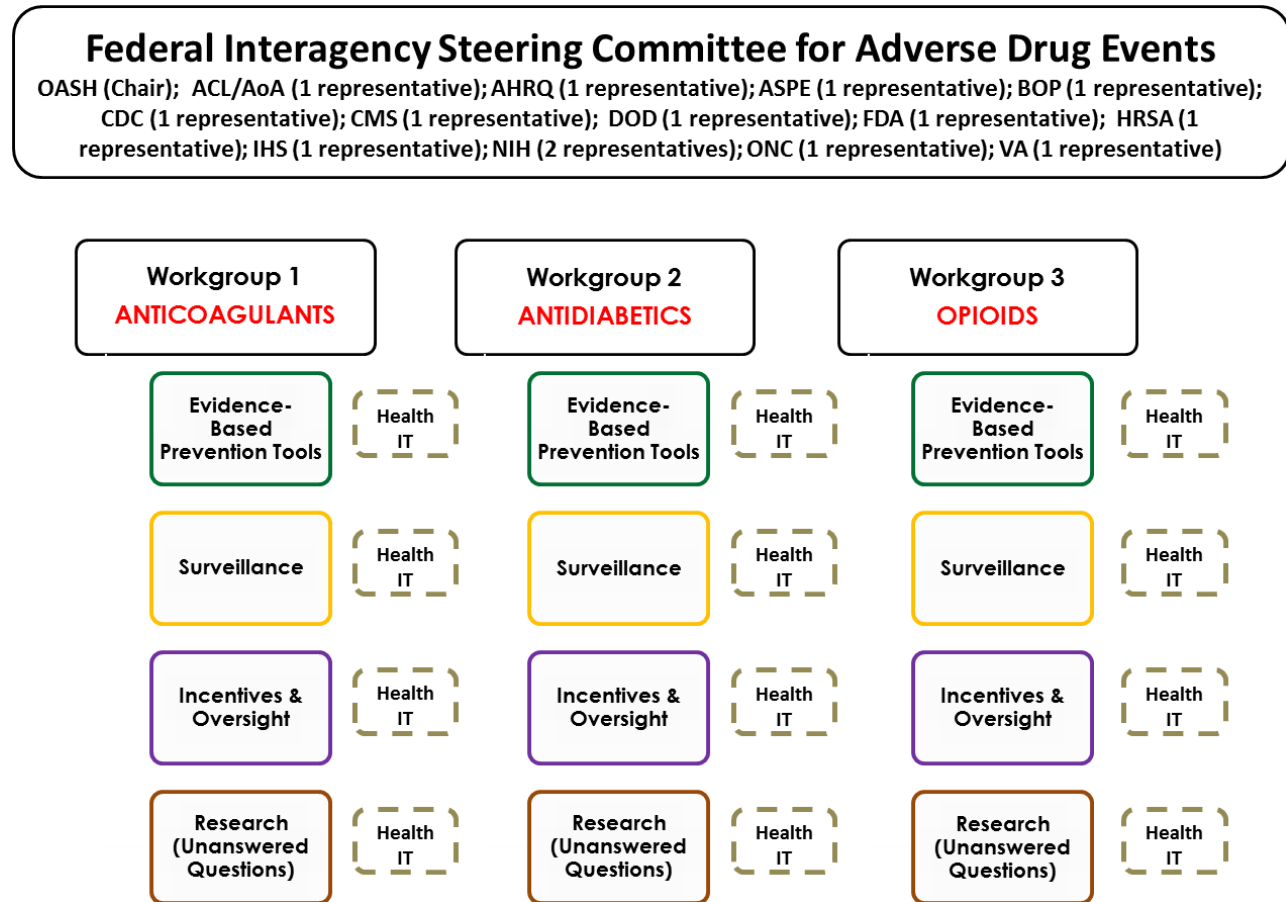
In September 2012, in response to the heightened awareness of the contributions of ADEs to health care-related harms and costs, the Office of the Assistant Secretary for Health (OASH) marshaled the wide-ranging and diverse resources of Federal partners to form an extensive interagency partnership, the Federal Interagency Steering Committee [Appendix A], whose goal would be to develop a National Action Plan for ADE Prevention, to be modeled after the National Action Plan to Prevent Healthcare-Associated Infections [37].

Structuring the ADE Action Plan

Given the substantial breadth and depth of ADEs and the complexity in attempting to address the full scope of medication-related harms, the members of the Federal Interagency Steering Committee determined that the ADE Action Plan would focus on those ADEs that (1) account for the greatest number of measurable harms, (2) can be effectively measured, and (3) are considered largely preventable. Among the drug classes considered for the ADE Action Plan targets were: anti-infectives, antineoplastics, anticoagulants, insulin/oral diabetes agents, opioids, and benzodiazepines. Owing to the morbidity and mortality associated with their harms and their well-established amenability for prevention, the Steering Committee selected *anticoagulants*, *diabetes agents (insulin and oral agents)*, and *opioids* as the three high-priority drug classes that would be initial targets for the ADE Action Plan.

Under the leadership of the Office of Disease Prevention and Health Promotion (ODPHP), the Federal Interagency Steering Committee established three separate Federal Interagency Workgroups (FIWs), each with a focus on one of the three high-priority drug classes. The FIWs initiated discussions to identify coordinated approaches to ADEs from these high-priority drug classes, specifically in the areas of surveillance, evidence-based prevention tools, incentives and oversight, and research (unanswered questions) [Figure 4]. In addition, each FIW considered health information technology (health IT) as a potential resource that could enhance the work in each of these areas.

Figure 4. Organizational Structure of the Federal Interagency Steering Committee and Workgroups for Adverse Drug Events



Abbreviations: Health IT = health information technology

The release of the ADE Action Plan should be viewed as only the beginning of a coordinated process that will result in stakeholders who are more engaged, aware, and knowledgeable of issues regarding the safe use of prescribed medications to prevent ADEs. Although the ADE Action Plan primarily reflects the efforts and resources of Federal Agencies, outlining ADE prevention goals and, more importantly, achieving ADE reductions and improving patient safety is neither complete nor feasible without further engagement of professional organizations. These include medical, nursing, pharmacy, and other allied health professionals; academia; consumer advocates; patients; and other private sector stakeholders. Consequently, the ODPHP, the Federal Interagency Steering Committee, and the FIWs for ADEs will continue to identify opportunities to engage these entities and gather their feedback. The goal is to use coordinated Federal partnerships, public and private sector collaborations, and aligned approaches to improve the quality and safety of health care, reduce health care costs, and improve the health and quality of life of millions of people in the United States. The Federal Interagency Steering Committee

anticipates that future iterations of the ADE Action Plan will provide both updates on progress in addressing the three high-priority ADE targets and expansion to other drug classes. Advances in surveillance systems will support the Federal Government's ability to monitor the impact of Federal coordination, as well as nationwide progress in reducing ADEs.

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SECTION 1

National ADE Action Plan Scope and Development

Scope of the National Action Plan for ADE Prevention

The *National Action Plan for Adverse Drug Events Prevention* addresses a defined group of ADEs that are considered to be common, clinically significant, preventable, and measurable; resulting from high-priority drug classes (i.e., anticoagulants, diabetes agents, and opioids); and occurring largely in high-risk populations (e.g., older adults). Preventable or ameliorable ADEs include medication errors (e.g., errors in the dose of drug administered) or adverse events that are outcomes resulting from harm caused by medical care that could have been mitigated in duration or severity by heightened monitoring or better health care management [1].

The ADE Action Plan is intended to address direct patient harms from prescribed medication use [2]. The ADE Action Plan seeks to identify, collate, and communicate opportunities and gaps within Federal systems and among external stakeholders. The ultimate goal is to strengthen and support health care systems and providers in their efforts to ensure the safest care of their patients with regard to preventing ADEs from a small group of high-priority drug classes. In addition, the ADE Action Plan provides some insights on current evidence-based best practices, so that greater consistency in the application of these practices can occur throughout the Nation, and identifies opportunities to drive improvement. The overriding focus of the ADE Action Plan begins with the most fundamental charge to health care systems and providers: “First, do no harm.”

Considering the breadth of harms resulting from medication use, the Federal Interagency Steering Committee decided to narrow the focus of the ADE Action Plan, with the intent of expanding the plan to a wider array of topics and drug classes in the future. Thus, the ADE Action Plan does not address circumstances beyond the therapeutic use of medications, such as illicit or recreational drug use, drug withdrawal, or use of medications in acts of intentional self-harm (e.g., suicide or suicide attempts). Other important public health issues, such as nonadherence to medication regimens, undertreatment of diseases, and underutilization of chemo-prophylaxis are also excluded from the focus of the ADE Action

Plan. The ADE Action Plan is not intended to serve as a clinical document or guideline, or a replacement for currently established, evidence-based clinical- and laboratory-guided strategies for preventing or reducing ADEs.

Framework for the National Action Plan for ADE Prevention

In designing an ADE Action Plan, the Steering Committee considered several models for ensuring a comprehensive focus in the effort to reduce ADEs. Leaders of each Federal Interagency Workgroup (FIW) agreed that the National Strategy for Quality Improvement (National Quality Strategy) addressed all of the challenges and incorporated all of the principles necessary to provide guidance in the development of ADE prevention strategies and advancement opportunities [3]. The National Quality Strategy (NQS), a requirement of the Affordable Care Act, is a nationwide effort to align public and private interests to improve the quality of health and health care for all Americans. Under the leadership of the Department of Health and Human Services (HHS), the NQS was developed using a collaborative process that solicited input from a wide range of stakeholders across the health care system. The strategy addresses health care delivered in all health settings and acknowledges the unique roles of the patient, his/her family, the health care provider, and the community (including State and local public health departments) in successfully achieving the goals. The NQS is defined by three aims (patient care, community health, and efficiency) and outlines six priorities to achieve these aims:

- 1) Safer Care
- 2) Informed Patient and Family Engagement
- 3) Communication and Care Coordination
- 4) Science-Driven Prevention and Treatment
- 5) Promoting Best Practices Within the Community
- 6) Innovative Delivery Models To Achieve Affordable Care

These priorities embody the principles and approaches that can effectively reduce ADEs and create a culture of safety around the effective use of medications. The first five NQS priorities have been used to frame each of the drug class-specific prevention sections of the ADE Action Plan. The sixth priority is included in the section on Incentives and Oversight Opportunities. One of the key principles in the ADE Action Plan is a focus on patient-centered care and patient participation in the delivery of health care.

This patient-oriented focus is essential to ensuring the successful management of chronic conditions that lead to the use of most prescribed medications. The NQS also addresses the unique nature of each patient’s clinical history and acknowledges that many patients experience multiple chronic conditions and may need a more comprehensive and coordinated approach to avoid ADEs.

Development Process for the National Action Plan for ADE Prevention

To develop the ADE Action Plan, the FIWs followed a systematic approach in which they

- Facilitated discussions among the Federal partners to identify opportunities and gaps in cross-agency coordination and alignment in four areas: surveillance, prevention, incentives and oversight policies, and research (unanswered questions)
- Conducted an initial environmental scan of existing Federal resources, medical literature, and clinical guidelines that address the four areas
- Evaluated and catalogued resources and initiatives to determine their pertinence to ADE prevention
- Performed a gap analysis to identify the strengths and weaknesses of current resources and develop recommendations to strengthen existing resources
- Engaged non-Federal subject matter expert consultants in the FIW discussions, so that they could contribute their expertise in addressing ADEs in each of the three drug class areas, define best practices, and provide recommendations for enhancing resources in ways that could support health care systems and providers

Consequently, the ADE Action Plan reflects the perspectives of a broad group of Federal Agencies and non-Federal subject matter expert consultants, and identifies opportunities to leverage existing resources and initiatives in the field of ADE prevention.

Organization of the National Action Plan for ADE Prevention

Using the model established by the Steering Committee for the National Action Plan To Prevent Healthcare-Associated Infections, the ADE Steering Committee identified key focus areas that corresponded to the most immediate areas for consideration in understanding and preventing ADEs associated with anticoagulants, diabetes agents, and opioids:

- **Surveillance**—Coordinate existing Federal surveillance resources and data to assess the health burden and rates of ADEs.
- **Prevention**—Share existing evidence-based prevention tools across Federal Agencies and with non-Federal health care providers and patients.
- **Incentives and Oversight**—Explore opportunities, including financial incentives and oversight authorities, to promote ADE prevention.
- **Research**—Identify current knowledge gaps and future research needs (unanswered questions) for ADE prevention.

Considerations for how health information technology (health IT) can be leveraged to advance ADE prevention are also incorporated throughout the ADE Action Plan. At the onset, the ADE Steering Committee and FIWs recognized the potential for health IT to support all aspects of the ADE Action Plan, including measurement, incentives, quality measure development and reporting, and prevention. Examples of how health IT can potentially support the ADE Action Plan are outlined in **Table 1**.

Table 1. Examples of How Health Information Technology Can Support Goals of the ADE Action Plan

Focus Area	Health IT Feature	Impact
Surveillance	Electronic data transmission	<ul style="list-style-type: none"> ▪ Real-time data reporting ▪ Reduced provider burden ▪ Improved patient access to health information
Prevention	Clinical decision support	<ul style="list-style-type: none"> ▪ Flowsheets ▪ e-prescribing ▪ Patient panels ▪ Implementation of clinical guidelines ▪ Sharing best practices
Incentives	Electronic health records	<ul style="list-style-type: none"> ▪ Meaningful Use
Research	Data repositories	<ul style="list-style-type: none"> ▪ Answer research questions ▪ Identify best practices ▪ Develop new research questions

Furthermore, leveraging health IT helps align the ADE Action Plan with goals outlined in the Federal Health Information Technology Strategic Plan. In November 2011, the HHS Office of the National Coordinator for Health IT (ONC) released the Federal Health Information Technology Strategic Plan, which identified “achieving rapid learning” as one of its five priority goals to advance by 2015 [4]. Through the establishment of a “Learning Health Care System,” health IT could aid in the identification

of effective interventions to prevent ADEs and accelerate integration of ADE surveillance and prevention strategies into clinical practice. A Learning Health Care System also has the potential to answer additional research questions to help advance the field of medication safety.

The Medicare and Medicaid Electronic Health Record (EHR) Incentive Program (e.g. Meaningful Use), which provides incentive payments for eligible professionals and hospitals that meet certain requirements in the use of an EHR, also represents a tremendous opportunity to leverage health IT resources to further the prevention of ADEs, while increasing opportunities for measuring progress. Currently, very few medication safety-specific targets are included in stage 2 of meaningful use for the EHR Incentive Program—and even fewer are included that address the high-priority medication classes associated with the most preventable morbidity in inpatient and outpatient settings [Table 2]. The current Core Measure requirements under Meaningful Use only address the need for documentation in the EHR of a current patient medication list, and the remaining medication safety-related measures are categorized under Clinical Quality Measures (CQMs), from which professionals and hospitals must select a preset number of measures on a menu list. These measures are less likely than Core Measures to be implemented. Furthermore, some of the medication safety-related CQMs do not uniformly reflect the most recent evidence on the sources of the highest burden of medication-related harms (e.g., use of “high risk” [or “Beers Criteria”] medications may not be optimal choices for older adults, but other medications are far more likely to result in ADEs) [5, 6, 7].

Table 2. 2014 EHR Incentive Program Core and Clinical Quality Measures Related to Medication Safety [8, 9, 10]

Core Measures	<ul style="list-style-type: none"> ▪ Use computerized provider order entry (CPOE) for medication orders (EP Core 1) ▪ Medication reconciliation (EP Core 14)
Clinical Quality Measures	<ul style="list-style-type: none"> ▪ Use of high-risk medications in the elderly (CMS156v1) (EP) ▪ Documentation of current medications in the medical record (CMS68v2) (EP) ▪ Warfarin Time in Therapeutic Range (TTR) (CMS179v1) (EP) ▪ VTE patients receiving unfractionated heparin with dosages/platelet count monitoring by protocol (or nomogram) (CMS eMeasure ID 109) (EH) ▪ VTE patients receiving warfarin discharge instructions (CMS eMeasure ID 110) (EH)

Abbreviations: EHR = electronic health record; EH = eligible hospital; EP = eligible professional; VTE = venous thromboembolism

Limitations of Health Information Technology

Throughout the ADE Action Plan, health IT is considered a tool, not a stand-alone solution for advancing ADE prevention efforts. Access to health IT is a valuable resource for health care providers and their patients across all health care settings, but there are a number of challenges associated with its

successful and more widespread adoption, such as costs of implementation and current limitations in data exchange and interoperability [11]. These limitations are acknowledged in the ADE Action Plan, and use of health IT is viewed as one of several strategies that can be implemented to enhance, not replace, delivery of optimal clinical care to prevent ADEs.

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SECTION 2

Surveillance Resources

This section of the *National Action Plan for Adverse Drug Event Prevention* (ADE Action Plan) reviews the ways the burden and rates of ADEs can be measured to monitor the progress in prevention at a population-based level.

Specifically, this section

- 1) Describes considerations for choosing surveillance data sources and metrics
- 2) Briefly identifies existing Federal ADE surveillance systems and reviews their operating characteristics
- 3) Addresses future considerations for optimizing Federal ADE surveillance efforts

Opportunities for advancing surveillance to drive improvement are then outlined within each of these sections.

Considerations for Choosing Surveillance Data Sources and Metrics

Public health surveillance is defined as the “ongoing, systematic collection, analysis, and interpretation of health data, essential to the planning, implementation and evaluation of public health practice, closely integrated with the dissemination of these data to those who need to know and linked to prevention and control” [1]. Indeed, public health surveillance metrics and systems may address a wide variety of issues, use a wide variety of methodologies, and be conducted in numerous settings.

To identify surveillance data sources and metrics that would be most useful for assessing the public health impact of ADEs, a number of issues should be considered.

General Surveillance System Considerations

Quantification Versus Signal Detection

Public health surveillance can be used to quantify the scope and magnitude of known public health issues (e.g., disease tracking/quantification). Public health surveillance can also be conducted to identify new or previously unrecognized health issues (e.g., outbreak/signal detection). In choosing surveillance metrics for the ADE Action Plan, emphasis should first be placed on quantifying clinically recognized ADEs already identified as having significant public health impact (i.e., ADEs from anticoagulants, diabetes agents, and opioids). Once metrics are established to quantify these clinically recognized ADEs, identifying ADEs from medication classes that may not be as readily amenable to recognition and documentation (i.e., signal detection) can then be addressed.

Active Surveillance Versus Passive Surveillance (Voluntary Reporting)

Active surveillance involves proactively collecting information on a health condition. Active surveillance traditionally involves collecting primary data from health records or patients but can also involve targeted queries of databases containing previously collected health information (e.g., administrative claims data, EHR data). In contrast, passive surveillance typically relies on clinicians or patients to voluntarily report information to a surveillance system. Although voluntary (i.e., spontaneous) reporting can be crucial for identifying outbreaks (e.g., clusters of ADEs of unusually high magnitude) or previously unidentified or underappreciated adverse effects, active surveillance is the method that is typically required to reliably quantify scope and magnitude of a health problem and to assess trends.

Actual Harms/Injuries Versus Potential Problems/Medication Errors

Health surveillance can be carried out to identify potential problems or risk factors that may lead to patient injury (e.g., medication errors that can potentially lead to ADEs, potential medication-related problems brought about by polypharmacy); however, potential problems and risk factors do not necessarily lead to actual patient harm. Identifying potential problems may be useful for screening patients and targeting prevention efforts, but surveillance of actual patient injuries (e.g., hemorrhage, hypoglycemia, and loss of consciousness) should be prioritized whenever possible to evaluate the national health impact of large-scale or population-based ADE prevention efforts.

Although efforts to reduce medication errors are important, surveillance for medication errors is complicated by a number of factors. Determination of error is often subjective, dependent on voluntary reporting, and assigns or at least implies fault or blame. In addition, the large majority of medication

errors do not cause patient harm [2, 3]. Error reporting may be critical for monitoring safety within individual facilities, but using error reporting for national ADE surveillance poses substantial challenges in evaluating the impact of large-scale or population-based ADE prevention efforts on actual harms.

Considerations Specific to ADE Surveillance

Adverse “Drug” Events

ADE surveillance requires identification of an injury (e.g., hemorrhage, hypoglycemia, loss of consciousness, and/or associated laboratory abnormalities) *and* attribution of that injury to drug exposure. This complicates the interpretation of surveillance based on administrative claims data (i.e., International Classification of Diseases ICD-9-CM or ICD-10-CM coding) because administrative coding was not designed with the intent of conducting ADE surveillance, is variably used, and lacks the necessary linkage of outcomes of interest (harms) to the drugs. Even if administrative data can be used to identify which individuals received a drug and experienced an event, it may not be possible to determine if the event was an ADE or an independent event. Diagnostic codes that incorporate attribution of an adverse event to a drug (i.e., External Causes of Injury Codes [E-codes]) are underutilized and have been found to lack sensitivity for capturing ADEs [4]. Laboratory data may aid in identifying some ADEs, but not all ADEs are amenable to capture by way of laboratory triggers, and laboratory data are not uniformly available across all Federal surveillance data sources.

One way to address the limitations of administrative claims data is reviewing clinical documentation, which can provide detailed data for determining drug-induced injuries. Because surveillance based on reviewing clinical documentation can be resource-intensive and may be more prone to subjectivity, ADE surveillance based on clinical documentation has utilized sampling techniques and algorithmic detection methods [5, 6]. In research studies, detailed clinical review has been used to identify the absence of a medication (because of patient nonadherence, undertreatment, or omission) as a medication-related problem [7]. Although important for optimizing medication management, conducting national surveillance for adverse events attributable to such issues as undertreatment or medication omission is beyond the initial scope of this particular ADE Action Plan.

Medication Use/Drug Denominators

Although assessing the number of ADEs is a primary goal of surveillance, the number of patients being exposed to those drugs is also a very important consideration. If drug use varies over time, metrics that include drug use may aid in the interpretation of ADE incidence or burden by placing these estimates in the context of rates. Although reductions in the absolute number of ADEs may be observed over time,

absolute reductions may not be evident if medication use increases. Therefore, examining evolving trends over time in such factors as prescribing, medication use, and chronic disease burden will be important in assessing the impact of large-scale or population-based ADE prevention interventions.

Severity

Like most health conditions, adverse drug events can vary in severity. A common approach to surveillance is to start conducting surveillance on more serious outcomes (e.g., deaths, hospitalizations, ED visits), followed by surveillance of less serious events (e.g., visits for nonemergent care, such as physician offices, and self-treated incidents).

Setting

Surveillance commonly focuses on a specific setting (e.g., hospital or clinic) and may then expand to other settings (e.g., ambulatory care, long-term care facilities). The setting where the ADE is treated often differs from the setting where the exposure occurs. Using the admitting diagnosis or the first diagnosis can assist in determining where the event occurred.

Scope

For an ADE Action Plan that is national in scope, nationally representative data are most applicable. Due to cost constraints, most surveillance systems that are national in scope utilize statistical sampling to project national estimates, using data from selected sites.

Timeliness

Timeliness of surveillance data is important to link data to prevention and control actions.

Prevention Patterns

Finally, not all events under surveillance must be patient harms. If the effectiveness of a prevention strategy has been established, surveillance, including by pharmacist review, could be used to measure penetration of that strategy and provide further context to changes in trends.

Federal Systems That Conduct ADE Surveillance

Federal surveillance systems vary in the populations surveyed, focus, geographic scope, data sources, and collection methods, as well as the definitions and approaches utilized to capture anticoagulant, diabetes agent, and opioid ADEs. Collectively, these systems point to opportunities and challenges for Federal partners to optimize ADE surveillance efforts that are addressed in further detail under each of

the high-priority drug sections that appear later in the ADE Action Plan. Currently available Federal surveillance systems for conducting ADE surveillance and their operational characteristics are summarized in **Appendix B**. Only Federally supported surveillance systems that are currently utilized to conduct ongoing ADE surveillance are included. These surveillance systems use three general methods: active identification of adverse events from clinical records, passive reporting of adverse events, or searches of administrative and/or clinical databases for codes or values indicating adverse events.

- 1) Active nationally representative adverse event-monitoring systems based on structured medical record review include
 - Agency for Healthcare Research and Quality (AHRQ) Medicare Patient Safety Monitoring System (MPSMS)
 - Centers for Disease Control and Prevention (CDC) National Electronic Injury Surveillance System—Cooperative Adverse Drug Events Surveillance System (NEISS-CADES)
- 2) Passive national adverse event-reporting systems include
 - Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS)
- 3) Systems that identify adverse events from administrative claims databases include
 - AHRQ Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS), State Inpatient Databases (SID), and Nationwide Emergency Department Sample (NEDS)
 - FDA Sentinel Initiative, Mini-Sentinel Pilot

Although they may not be nationally representative, the following Federal integrated health networks also conduct adverse event surveillance and may incorporate all three general methods:

- Bureau of Prisons (BOP) quality improvement programs
- Department of Defense (DOD) Patient Safety Reporting System
- Indian Health Service (IHS) Resource and Patient Management System (RPMS-EHR)
- Veterans Health Administration (VHA) Integrated Databases/Adverse Drug Event Reporting System (VA ADERS)

The Federal passive (voluntary) reporting systems, such as FDA’s FAERS, NIH’s Drug-Induced Liver Injury Network (DILIN), and VHA’s VA ADERS, were constructed to identify (and have identified many) signals of previously unrecognized, underappreciated, or rare ADEs. To do so, they were designed to include

reports in which the adverse event may or may not be related to the identified drug. They are not designed for complete accounting of ADEs or calculating population-based estimates. Patient Safety Organizations (PSOs) are independent, non-Federal voluntary reporting systems authorized under the Patient Safety and Quality Improvement Act of 2005 that may also be useful for signal detection and local reporting, but these organizations are not national in scope and may not focus on ADEs.

Federal active surveillance systems can provide estimates and rates of ADEs based on data compiled from millions of administrative claims. AHRQ's HCUP and FDA's Sentinel Initiative utilize administrative claims and ICD-9-CM codes to enumerate the risks of medication-related harms. However, claims data have limited ability to control for certain variables (e.g., co-morbidities) that may confound the link between drugs and certain outcomes and to assess medication adherence. Currently, Sentinel covers more than 125 million lives, which does not constitute a nationally representative sample, but for specific studies, FDA's Sentinel Initiative has the potential to access health records to confirm coded data or provide additional data. HCUP data can be extrapolated to provide national estimates, as well as regional- and State-level estimates for specific common ADEs.

By using structured clinical record review, AHRQ's MPSMS is able to provide population-based national estimates and rates for specific ADEs (ADEs due to anticoagulants and diabetes agents) in hospitalized patients and to examine correlations with other types of adverse events among the same patients (e.g., pressure ulcers, infections). CDC's National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project can provide annual national estimates of emergency department visits and emergent hospitalizations attributed to harms from outpatient therapeutic drug use (excluding abuse or self-harm). Strengths of the system include its case identification method of reviewing free-text narratives of each case, which may provide additional contextual information on medication-related overdoses that are related to therapeutic use and errors. However, because both MPSMS and NEISS-CADES utilize statistical sampling from a national frame, regional or State-based estimates cannot be calculated or tied to local quality improvement efforts.

CDC's National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) provide annual national estimates on the utilization of ambulatory medical care in the United States. [8]. These sample surveys of visits can capture outpatient ADEs, as reported by E-codes found in the ICD-9-CM. Although these surveys are useful for calculating overall estimates of outpatient ADEs [9, 10], they are limited in the information they can provide on ADEs because of the small sample size of such visits in NAMCS and NHAMCS. CDC plans to integrate NHAMCS National

Hospital Discharge Survey and the Drug Abuse Warning Network into the National Hospital Care Survey, which will provide the ability to link patients within the same sampled hospital to outside data sources [11].

VHA's active surveillance system focuses on quality improvement for a selected population, utilizing the VHA's inpatient and outpatient care settings. The system comprises a comprehensive Drug Use Evaluation (DUE) program and a Medication Use Evaluation Tool (MUET), which identify patients at high risk for ADEs on the basis of pharmacy, laboratory, and diagnostic triggers. The system is an example of using facility-level surveillance data to assist health care providers in real-time decisionmaking to mitigate risks of ADEs in patients.

The BOP, DOD, VHA, and IHS also have systems that leverage both passive and active surveillance strategies, with a focus on quality improvement for the populations under their care (**Appendix B**).

Figure 5 highlights the strengths, weaknesses, opportunities, and threats of the Federal systems that can be used to conduct ADE surveillance.

Figure 5. Strengths and Limitations of Federal Systems That Conduct ADE Surveillance [12]

<p>S: Strengths</p> <ul style="list-style-type: none"> • Inpatient and outpatient settings addressed • Majority capture ADEs from high-priority drug targets (i.e., anticoagulants, diabetes agents, opioids) • Flexibility 	<p>W: Weaknesses</p> <ul style="list-style-type: none"> • Some critical settings unaddressed (e.g., long-term care facilities, transitions of care) • Highly variable sensitivity, specificity, PPV, and NPV of diagnostic and procedural coding (i.e., ICD-9-CM and CPT) in capturing ADEs (i.e., not designed or intended for ADE surveillance) • Variable in their ability to link outcomes (harms) of interest to drugs • Timeliness
<p>O: Opportunities</p> <ul style="list-style-type: none"> • Harnessing of large datasets through public-private collaborations (e.g., FDA Sentinel Initiative) • Leveraging of linked EHRs and new communication technologies 	<p>T: Threats</p> <ul style="list-style-type: none"> • Funding to support ongoing analyses of surveillance data

Abbreviations: ADE = adverse drug event; CPT = Current Procedural Terminology; EHRs = electronic health records; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; PPV = positive predictive value; NPV = negative predictive value

Future Considerations for Optimizing Federal ADE Surveillance Efforts

Existing Federal systems provide a starting point for national surveillance of adverse events from anticoagulants, diabetes agents, and opioids. Future considerations to optimize Federal ADE surveillance efforts are outlined in the following sections.

Refine and improve existing national systems

National surveillance using population-based sampling or administrative data is an efficient way of collecting nationally representative data on ADEs. Because administrative data collection and coding systems were not designed for the primary intent of ADE surveillance, mapping existing codes (e.g., ICD) and data collection (e.g., present on admission) to ADEs should be validated. However, it may be necessary to revise coding systems with ADE quantification in mind or consider alternative approaches to support better documentation of ADEs similar to the current approach used to document drug allergies. NEISS-CADES data are currently used to chart progress of the Healthy People 2020 objectives to reduce emergency visits for overdoses of oral anticoagulants and injectable diabetes agents (i.e., insulin). AHRQ is currently developing measures for specific (drug-type) ADEs that build on the current MPSMS ADE definitions, for use in the new Quality and Safety Review System (QSRS). There are ongoing opportunities to refine and validate the identification of specific ADEs from administrative and clinical databases. In addition, data on medication use that can be used to calculate ADE rates are needed to interpret whether changes in the number of ADEs may be caused by safety changes or changing patterns of medication use.

Opportunities for Clinical Setting Surveillance

Although national monitoring is useful for identifying burden and monitoring progress, actually preventing ADEs requires action by individual providers and patients at the health system level and, thus, an understanding of facility-level burden and trends in ADEs. The National Healthcare Safety Network (NHSN) is one example of how individual facility-level reporting of health care-associated infections (HAIs) has facilitated improved understanding of HAI burden, enabled facility-level prevention efforts, and driven national-level improvements in HAI burden [13]. Refining the next version of AHRQ Common Formats for reporting specific ADEs could provide another opportunity to facilitate reporting, analysis, and reduction of ADEs in individual facilities across the Nation. Quality and safety initiatives in anticoagulation management, hypoglycemic event monitoring, and opioid optimization that incorporate surveillance may also provide the opportunity for innovations. Surveillance innovations may be found in non-Federal collaboratives [14, 15] as well as in Federal integrated health networks.

Role of Federal Agencies That Provide Direct Patient Care

Federal Agencies that provide care for specific populations (e.g., BOP, DOD, HRSA, IHS, VHA) play an important role in facilitating the infrastructure necessary for monitoring ADEs at regional or facility levels, in rural settings, and in low-resourced settings. Collaborating on monitoring methods across Federal Agencies that directly care for patients at risk for ADEs, as well as collaborating with non-Federal partners such as PSOs, could aid the efficacy and efficiency of efforts. This would require an administrative structure to foster such ongoing collaborations and communication in this area.

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SECTION 3

Prevention Approaches

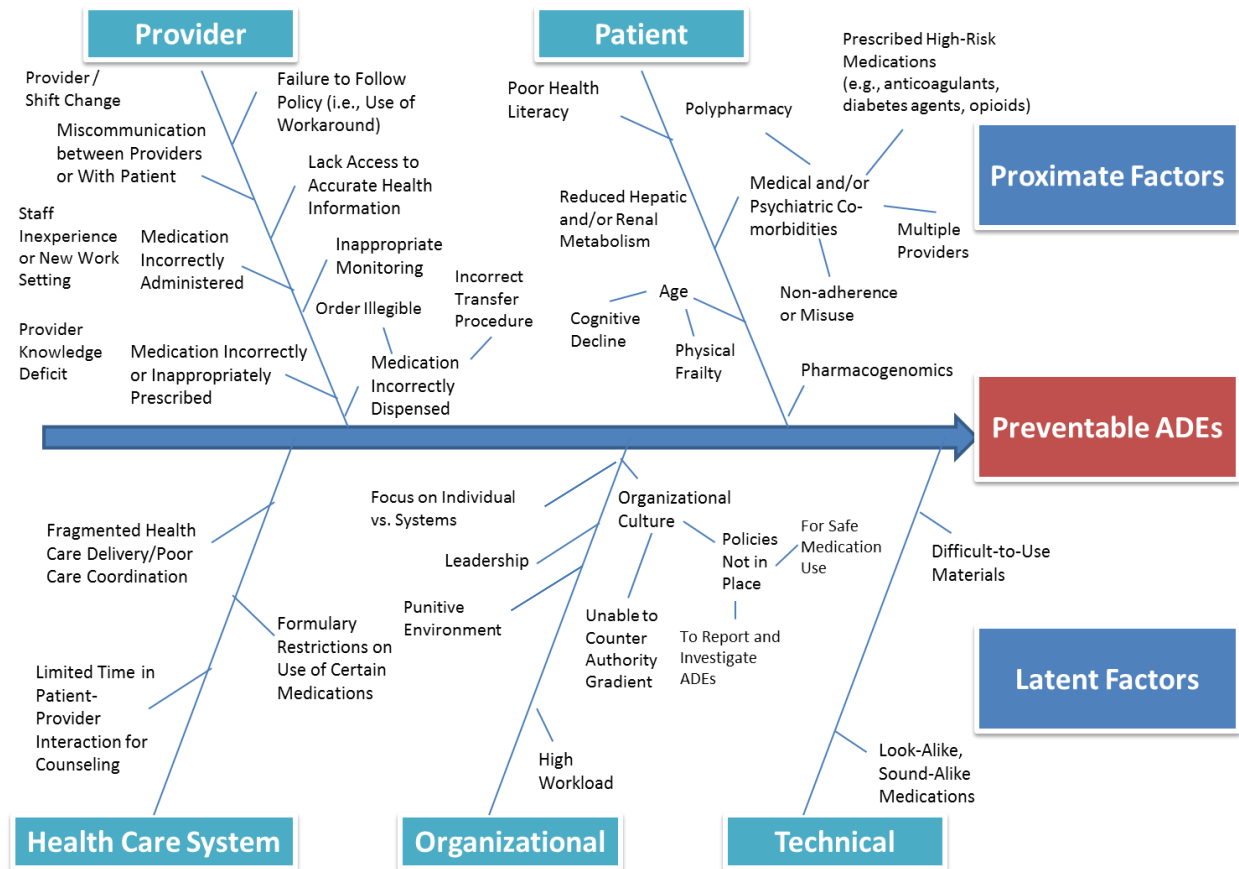
Multiple factors may contribute to ADEs that occur in inpatient, outpatient, and other health care settings (e.g., long-term care facilities, group homes), or during care transitions. The delivery of safe health care depends on the creation of a reliable health care system that considers systems, organizational, technical, provider, and patient factors that may contribute to harm.

Key Determinants of Preventable ADEs

The Joint Commission patient safety event taxonomy model helps to potentially identify key determinants of ADEs [1]. This model categorizes root causes of patient safety events into proximate (e.g., human) and latent (e.g., organizational and system) factors.

As part of a continuous quality improvement approach to health care, The Joint Commission requires a root cause analysis to investigate factors that contribute to a sentinel event [2]. The fishbone diagram in **Figure 6** presents selected proximate and latent determinants of preventable ADEs. The literature suggests that ADEs in all health care settings may arise from a combination of patient, provider, and health care system factors. Although the key determinants presented in Figure 6 may not be implicated in all health care settings or patient situations, they should be considered in root cause analyses, as any one of the determinants may lead to an ADE.

Figure 6. Fishbone Diagram: Select Determinants of Preventable Adverse Drug Events



Proximate factors that contribute to ADEs include those that involve the patient and/or provider. Considering the patient-centered care approach supported by the National Quality Strategy, it is important to note patient factors that may contribute to ADEs. A number of proximate factors place older adults at particular risk for ADEs. For example, altered pharmacokinetics, use of multiple medications, and potential for medication mismanagement due to cognitive decline or physical frailty contribute to ADEs in older adults [3, 4, 5]. Patients with multiple chronic conditions are also more likely to be prescribed more than five medications, many of which may be high-risk medications and increase the risk of drug–drug interactions [3]. Older adults also frequently have multiple providers, which may result in uncoordinated or poorly coordinated care [5]. In addition, older adults are at increased risk for nonadherence or misuse of medications [6, 7].

Other proximate factors that contribute to individual/patient risk of ADEs include inherited factors and health literacy. Inherited factors can affect the kinetics and dynamics of numerous drugs and may include genetic variation in genes for drug-metabolizing enzymes, drug receptors, and drug transporters,

which have been associated with individual variability in the toxicity of drugs [8]. Poor health literacy also has been implicated as a contributing factor to ADEs [6].

Provider factors that may contribute to ADEs involve physicians, pharmacists, nurses, and caregivers who are certified to administer medication. As indicated in **Figure 6**, these may include errors in medication prescribing, dispensing, or administration [6, 7, 9, 10].

Once proximate factors are identified, emphasis should be on system-related factors that may have contributed to the ADE [3, 6, 10, 11]. Latent key determinants that may contribute to ADEs are systemic, organizational, or technical. Systemic factors may include failure to incorporate key health literacy principles [12], limited provider time to adequately explain information [6], poor coordination of care [7, 13], or formulary restriction on use of certain types of medications (particularly opioids) [14]. Organizational factors include those involving the institutional patient safety culture, leadership, and high provider workload [2, 3, 9]. Lastly, technical factors are those related to medical product design and include materials or medications that look similar, or materials that are difficult to use [2].

Organizations may use this model of key determinants of ADEs to ensure that patient, provider, technical, organizational, and systemic factors are considered in efforts to prevent ADEs. Organizations may conduct a careful root cause analysis of ADEs that identifies underlying causes and potential targets for intervention, with the goal of preventing their recurrence. By determining and verifying probable causal pathways that led to the adverse drug event, root cause analysis allows organizations to identify appropriate corrective and/or preventive actions, as well as to encourage the development of a culture of safety. Implementing such quality improvement initiatives is in direct support of the National Quality Strategy, which strives to make health care safer for all Americans.

Affordable Care Act—Health Care Delivery Models

Several innovative health care delivery models authorized in the Affordable Care Act are crucial to improving the sustainability of the health care system, reducing costs, and improving quality of care for patients. Models that potentially can be leveraged to further target high-priority ADEs include: patient-centered medical homes (PCMHs), Accountable Care Organizations (ACOs), and team-based health care. Summaries of these models can be found in **Appendix C**.

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SECTION 4

Incentives and Oversight Opportunities

The U.S. Department of Health and Human Services (HHS)—specifically, the Centers for Medicare and Medicaid Services (CMS)—has a variety of tools within its statutory and regulatory authority to support the prevention of ADEs [Appendix D]. These tools can be broadly classified as

- Regulatory oversight activities (including Conditions of Participation (COPs), accreditation, and survey and certification)
- Value-based purchasing (VBP) programs and other financial incentives
- Transparency and associated incentives
- Medicare and Medicaid initiatives

This section discusses in detail the various ways in which these tools and initiatives are being used to support the Nation's efforts to prevent ADEs.

Regulatory Oversight

The CMS developed Conditions of Participation (CoPs), Conditions for Coverage (CfCs),ⁱ and long-term care facility (LTCF) requirementsⁱⁱ that hospitals and other providers and suppliers must meet to participate in the Medicare and Medicaid programs. These Federal health and safety requirements are intended to ensure that high-quality care is provided to all patients and residents. All Medicare- and Medicaid-participating providers and suppliers for which there are CoPs/CfCs are required to be in compliance at all times. Compliance is assessed by CMS Federal surveyors, State Survey Agencies (SAs), federally contracted surveyors, and national accreditation organizations (AOs) having CMS-approved

ⁱ More information on the CoPs and CfCs is available at: <http://www.cms.gov/Regulations-and-Guidance/Legislation/CFCsAndCoPs/index.html>

ⁱⁱ More information on the requirements for LTCFs is available at: <http://www.cms.gov/Regulations-and-Guidance/Legislation/CFCsAndCoPs/LTC.html>

Medicare accreditation programs. CMS has regulatory requirements and interpretive guidelines related to the prevention of ADEs for numerous health care providers and suppliers. The following section describes some of these ADE-related regulations and guidelines.

Regulations and Interpretive Guidelines

Hospitals

The hospital CoPs address ADEs in two ways. First, in accordance with accepted standards of practice, the CoPs address the establishment and implementation of policies and procedures to minimize errors related to drugs and to internally report errors when they occur. Second, the CoPs address the hospital's internal quality assessment and performance improvement process to track adverse events, including ADEs; to analyze their causes; and implement preventive actions, including feedback and learning throughout the hospital. In addition, the CMS survey and certification interpretive guidelines provide a vehicle for a more specific discussion of best practices in ADE prevention and tracking.

Critical Access Hospitals

The critical access hospital (CAH) CoPs focus on internal reporting of adverse drug reactions and drug administration errors in a manner similar to that required for traditional acute care hospitals.

Long-Term Care (LTC)

The LTC regulations that apply to institutional settings such as nursing homes contain many drug-related requirements. Specifically, the regulations state that an LTC facility must ensure that it is free of medication error rates of 5 percent or greater and that residents do not experience any significant medication errors. The LTC facility regulations also require that each resident's drug regimen be free from unnecessary drugs, and focus on the adverse consequences associated with the use of a wide variety of drugs. CMS provides extensive background and clinical information to improve the body of knowledge surrounding the prescription and administration of drugs in the LTC setting. In particular, CMS provides specific use and monitoring guidelines for anticoagulants, diabetes medications, and opioids.

CMS requires that LTC facility residents be free from unnecessary drugs and, to minimize adverse consequences related to drug therapy to the extent possible, the regulations also require that the drug regimen of each resident be reviewed at least once a month by a licensed pharmacist. Furthermore, the regulations require that any irregularities be reported to the attending physician and the director of nursing, and that facility staff act on these reports. The interpretive guidelines also discuss the drug-

related risks that are involved in care transitions, a period when drugs are often added, discontinued, omitted, or changed, and how these increased risks necessitate the need for safeguards, such as drug regimen review.

Home Health Agencies

The home health agency CoPs seek to prevent ADEs by ensuring that each patient receives a drug regimen review as part of a comprehensive assessment that is conducted at the time the patient begins home health care. The drug regimen review is updated at least once every 60 days. The review has a particular focus on identifying potential adverse effects, drug interactions, duplicate drugs, and issues related to patient noncompliance with the prescribed drug regimen. The interpretive guidelines for this section state that, if any potential adverse effects and/or reactions are identified, the physician must be notified. Because orders change frequently, the home health agency staff must be aware of any and all changes as they occur, constantly reevaluating medications, compliance, interactions, and effectiveness of the drug regimen.

Survey and Certificationⁱⁱⁱ

The survey and certification (S&C) program is designed to ensure that providers and institutional suppliers comply with the CoPs/CfCs. When surveyors identify a deficiency, the provider or supplier is required to take prompt action to ensure compliance, typically involving a plan of correction, which must be reviewed and found acceptable by CMS, either through the survey agency or the accreditation organization, if applicable, and then appropriately implemented.

Value-Based Purchasing Financial Incentives

Value-based purchasing is a mechanism that uses financial incentives to encourage all levels of health care providers to improve quality of care.

Hospital Pay-for-Reporting^{iv}

The Hospital Inpatient Quality Reporting (Hospital IQR) Program requires subsection (d) hospitals paid under the Inpatient Prospective Payment System (IPPS) to report on different quality measures,

ⁱⁱⁱ More information on the S&C program is available at: <http://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/index.html?redirect=/surveycertificationgeninfo/>

^{iv} More information on the Hospital IQR program is available at: <https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/HospitalRHQDAPU.html>

including process, structure, outcome, patients' experience of care, efficiency, and cost efficiency measures. Performance on quality measures is publicly reported on the CMS Hospital Compare Web site.^v In implementing the Hospital IQR Program, CMS expects the measure set to continue to evolve on the basis of factors such as program needs and high-priority areas. Through the Hospital IQR Program, CMS has the authority to adopt quality measures addressing ADEs. Measures adopted for the Hospital IQR Program may also be adopted for use in other CMS initiatives linking quality to payment, such as the Hospital Value-Based Purchasing and the Hospital-Acquired Condition Reduction Programs.

CMS Demonstration Projects and Models

The CMS Innovation Center develops and tests innovative payment and service delivery models. Within this center, there are at least five programs that address ADEs; they are described in the following sections.

Health Care Innovation Awards (HCIA)^{vi}

The Health Care Innovation Awards provide funding to organizations that are implementing the most compelling new ideas designed to deliver better health, improved care, and lower costs to people enrolled in Medicare, Medicaid, and the Children's Health Insurance Program (CHIP). Of the 107 currently funded projects, 48 include a focus on medication reconciliation or medication management services.

Pioneer Accountable Care Organizations (ACO) Model^{vii}

The Pioneer Accountable Care Organizations (ACO) Model is designed to work in coordination with private payers by aligning provider incentives to improve quality and health outcomes, while achieving cost savings. The Pioneer ACO Model supports measuring and reducing ADEs, including efforts to standardize decision support for safe medication management (e.g., medication reconciliation, allergy checks, drug interaction checks, and checks for duplicate or contraindicated therapy). Specifically, one Pioneer ACO measured and reported safety events of all types via safety reporting systems at each site within its network. In regard to measurement approaches, system process measures (e.g.,

^v <http://www.medicare.gov/hospitalcompare/search.html>

^{vi} More information on the Health Care Innovation Awards is available at: <http://innovation.cms.gov/initiatives/Health-Care-Innovation-Awards/>

^{vii} More information on the Pioneer ACO Model is available at: <http://innovation.cms.gov/initiatives/Pioneer-ACO-Model/>

implementation of barcoding, computerized order entry, electronic prescribing, and anticoagulation management services) were a primary focus.

Multi-Payer Advanced Primary Care Practice (MAPCP)^{viii}

The Multi-Payer Advanced Primary Care Practice (MAPCP) demonstration includes multipayer reform initiatives that eight States are conducting to make advanced primary care practices more broadly available. Two participating States include a focus on medication safety. In one State, networks of community-based practices focus on medication safety through the provision of clinical pharmacy and care management services. The focus is on high-risk patients, including those with multiple co-morbid conditions and those at risk for complications from polypharmacy. Nurse care managers and clinical pharmacists conduct medication reviews and reconciliations to identify and rectify expired, duplicate, or incorrectly dosed medications. These providers also are tasked to identify reasons why patients might not be taking their medicines as prescribed and to counsel patients taking multiple medications.

The other State uses an advanced health IT system that provides patient-level information on pharmacy claims and medication history for point-of-care activities. The system also can generate population-based reports to identify patients who may benefit from clinical pharmacy and care management services. This system captures descriptions of clinical pharmacists' activities and findings, previously identified drug–drug interactions, expired medications, reconciled medications, suggested formulary medications, and changes to lower cost medication. In addition, providers at practices with advanced electronic health records (EHRs) receive alerts for patients who need refills, in order to keep track of patients' medications and to identify duplications and drug–drug interactions.

Community-Based Care Transitions Program^{ix}

The goals of the Community-Based Care Transitions Program (CCTP) are to improve transitions of high-risk Medicare beneficiaries from the inpatient hospital setting to other care settings, including home. All the CCTP sites provide medication reconciliation, and two are providing a separate pharmacy intervention, whereby a pharmacist meets with the beneficiary, reviews the current medication regimen, and attempts to optimize the regimen.

^{viii} More information on the Multi-Payer Advanced Primary Care Practice is available at: <http://innovation.cms.gov/initiatives/Multi-Payer-Advanced-Primary-Care-Practice/>

^{ix} More information on the Community-based Care Transitions Program is available at: <http://innovation.cms.gov/initiatives/CCTP/>

Partnership for Patients^x

The Partnership for Patients is a public–private partnership working to improve the quality, safety, and affordability of health care for Medicare, Medicaid, and CHIP beneficiaries—and, by extension, all Americans. The Partnership involves physicians, hospitals, employers, patients and patient advocates, and the Federal and State Governments to achieve two main goals:

- 1) Making care safer by reducing hospital-acquired conditions
- 2) Improving care transitions by decreasing preventable complications during transitions from one health care setting to another

The Partnership has identified 10 core safety areas of focus, including adverse drug events. Working with more than 3,700 hospitals across the United States, the program aims to eliminate approximately 1.8 million avoidable injuries.

Medicare-Medicaid Beneficiaries

The Medicare-Medicaid Coordination Office (MMCO), partnered with the Center for Medicare & Medicaid Innovation (CMMI), has launched the “Initiative To Reduce Avoidable Hospitalizations Among Nursing Facility Residents.”^{xi} One goal of this initiative is to improve beneficiary safety by better coordinating the management of prescription drugs, to reduce the risk of polypharmacy, improve medication reconciliation, and prevent adverse drug events.

Hospital Value-Based Purchasing and the Affordable Care Act^{xii}

With the 2010 passage of the Affordable Care Act, CMS launched the Hospital Value-Based Purchasing (HVBP) Program, which provides powerful incentives, both financial and nonfinancial, to improve quality of care. CMS is considering whether to propose ADE measures for future updates to the program to reward high-quality performance.

^x More information on the Partnership for Patients is available at: <http://partnershipforpatients.cms.gov/>

^{xi} More information on the Initiative to Reduce Avoidable Hospitalizations Among Nursing Facility Residents is available at: <http://innovation.cms.gov/initiatives/rahnfr/>

^{xii} More information on the Hospital Value-Based Purchasing Program is available at: <http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/hospital-value-based-purchasing/index.html?redirect=/hospital-value-based-purchasing>

Medicare and Medicaid EHR Incentive Programs^{xiii}

The Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009 authorized CMS to establish the Medicare and Medicaid EHR Incentive Programs for meaningful use of certified EHR technology (Meaningful Use). In order to qualify for Meaningful Use incentive payments, each provider category (eligible professionals, eligible hospitals, and critical access hospitals) must meet different functional objectives.

Providers must report four measures related to ADEs:

- Maintain active medication list
- Maintain active medication allergy list
- Implement drug–drug and drug–allergy interaction checks
- Implement clinical decision support rules

Also, there are specific measures that address the prevention or reduction of ADEs related to the three main drug classes (anticoagulants, opioids, and diabetes agents). In the future, additional measures can be developed and electronically specified for a more diverse range of ADE prevention and monitoring measures.

Because existing EHR specifications that address high-priority ADE targets were limited, at the request of the HHS Office of the National Coordinator for Health IT (ONC), the FIWs for ADEs initiated discussions among the Federal partners to identify possible requirements that the EHR Incentive Program might consider to leverage EHR capabilities to further the state of ADE prevention and monitoring. Recommendations from the three FIWs related to the potential for Meaningful Use to advance the prevention of ADEs are addressed in the drug class-specific Incentives and Oversight sections.

Physician Quality Reporting System^{xiv}

The Physician Quality Reporting System (PQRS) provides a series of incentive payments to eligible professionals (including physicians, physician assistants, and nurse practitioners) for meeting satisfactory reporting criteria on quality measures. Beginning in 2015, those who do not meet the

^{xiii} More information on the Medicare and Medicaid EHR Incentive Programs is available at: http://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/Meaningful_Use.html

^{xiv} More information on the Physician Quality Reporting System is available at: <http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/PQRS/index.html>

criteria will receive negative payment adjustments. In an effort to align with Meaningful Use, PQRS introduced two measures that address ADEs for the 2014 Program Year:

- CMS68 (NQF #0419)—Documentation of Current Medications in the Medical Record
- CMS179—ADE Prevention and Monitoring: Warfarin Time in Therapeutic Range

The PQRS historically held an annual call for measures during which stakeholders could submit their quality measures for consideration in the program. Beginning in 2014, PQRS will move to a rolling call for measures so that developers will be able to submit measures for inclusion in the program on an ongoing basis. Through the call for measures and continuing alignment with other quality programs, additional ADE measures could be introduced in the PQRS.

Physician Feedback Program/Value-Based Payment Modifier^{xv}

The goals of the Physician Feedback/Value-Based Payment Modifier Program are to improve Medicare beneficiary health outcomes and experience of care by using payment incentives and transparency to encourage higher quality, more efficiently provided health care services. The Physician Feedback Program provides confidential, comparative performance reports to physicians and clinician groups that measure the resources involved in furnishing care and the quality of care provided to Medicare beneficiaries. Beginning in 2015, CMS is also required to apply a separate, budget-neutral, value-based payment modifier to the Physician Fee Schedule based upon a physician's or clinician group's quality of care furnished as compared to cost during a performance period. CMS utilizes PQRS measures within the quality component of the value-based payment modifier calculation. These measures may include quality measures related to patient safety and any adverse drug event. CMS anticipates continued enhancements to the quality and cost measures for the value-based payment modifier as additional quality and resource use measures become available. This also would apply to any newly developed ADE measures.

^{xv} More information on the Physician Feedback/Value Based Payment Modifier Program is available at: <http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeedbackProgram/index.html?redirect=/PHYSICIANFEEDBACKPROGRAM>. The physician compare tool is accessible at: <http://www.medicare.gov/PhysicianCompare/search.html>

Transparency and Associated Incentives

Public reporting of health care quality data supports transparency, encourages provider accountability, and provides consumers access to information that will help them make more informed health care decisions.

Hospital Compare^{xvi}

The measures currently reported on the Hospital Compare Web site include those that are reported under the Hospital Inpatient and Hospital Outpatient Quality Reporting Programs (Hospital Pay for Reporting), those used in the calculation of incentives under the Hospital Value-Based Purchasing Program, the Hospital-Acquired Conditions Program, the Hospital Readmissions Reeducation Program, and additional measures that many hospitals voluntarily report. Some of these measures are related to reduction of ADEs.

Physician Compare^{xvii}

The Affordable Care Act (2010) required CMS to establish a Physician Compare website that contains information on physicians enrolled in the Medicare program as well as other eligible professionals who participate in the Physician Quality Reporting System. The specific measures posted are addressed annually through rulemaking.

Related Initiatives Addressing ADEs

In addition to the programs detailed above, CMS also oversees a variety of additional programs that have the potential to advance nationwide efforts to prevent ADEs.

Quality Improvement Organizations^{xviii}

The Quality Improvement Organization (QIO) Program is a network of organizations staffed with physicians, pharmacists, nurses, technicians, and statisticians who are experts in health care quality. Currently, each QIO

^{xvi} More information on Hospital Compare is available at: <http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/HospitalCompare.html>. The hospital compare tool is accessible at: <http://www.medicare.gov/hospitalcompare/search.html>

^{xvii} More information on Physician Compare is available at: <http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/physician-compare-initiative/>

^{xviii} An overview of the Quality Improvement Organization program and the programs outlined in its current statement of work is available at: <http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/QualityImprovementOrgs/index.html?redirect=/qualityimprovementorgs>

is responsible for a U.S. State, territory, or the District of Columbia. The current contract (also known as the 10th Statement of Work) focuses on four aims: (1) Improving individual patient care, (2) beneficiary and family-centered care, (3) integrating care for populations and communities, and (4) improving health for populations and communities. The contract also focuses on the use of learning and action networks to spread and sustain positive results. Specific QIO programs related to ADE efforts are outlined below.

Reducing Adverse Drug Events Aim

Under the current contract, CMS requires QIOs to contribute to the aim of reducing and preventing ADEs and to provide medication-related quality improvement intervention strategies to health care providers, practitioners, Medicare Advantage organizations, and prescription drug sponsors. QIOs are tasked to participate in the Patient Safety and Clinical Pharmacy Services Collaborative (PSPC) as part of this aim.

The PSPC was initiated by the Health Resources and Services Administration (HRSA) and CMS, and is now a CMS-directed initiative that integrates evidence-based clinical pharmacy services into the care and management of high-risk, high-cost, and complex patients. As part of the PSPC, QIOs recruit and form teams of community health care providers and Medicare beneficiaries to transform their health care delivery systems to reduce ADEs. The QIOs also target specific populations of focus, including beneficiaries taking diabetes agents, anticoagulants, and antipsychotics.

Nationally, the QIO program has developed innovative approaches and developed best practices to reduce ADEs across several care settings. For example, one QIO has established a multidisciplinary statewide anticoagulation coalition dedicated to improving anticoagulation quality and safety using standardized dosing algorithms, root-cause analysis of potential ADEs, and connecting outcomes such as readmissions to ADEs. Another QIO has done extensive work on measure development related to ADEs that are suitable for national programs. Measure development efforts included both process and outcome measures related to the use of anticoagulants and diabetes agents. The National Quality Foundation (NQF) has endorsed two anticoagulant-related measures (NQF 555 and NQF 556) for use in the ambulatory care setting.

In addition to implementing interventions and forming community team coalitions to reduce ADEs and improve overall medication therapy management, QIOs are required to track and report measures. Measures reported by QIOs include, across time, the overall rate of ADEs, the rate of potential ADEs,

and specific measures targeting three areas of focus: anticoagulants, diabetes agents, and antipsychotic medications.

Improve Care Transitions and Decrease Readmissions

The Integrating Care for Populations and Communities Aim (ICPCA) under the 10th Scope of Work includes interventions to improve effectiveness of pharmacotherapies that can be a driver of poor care transitions and increased readmissions. Improving the effectiveness of pharmacotherapy includes supporting a patient’s understanding of appropriate medication use and potential risk for adverse events, adherence to medication regimens, and detection of adverse events and overuse or underuse. These interventions also are meant to improve transfer of patient care between providers and to improve information transfer between clinical settings.

Regional Efforts

Regional Chief Medical Officer Efforts

In response to the recommendation to enhance efforts to identify and reduce ADEs in all health care settings, the regional CMS Chief Medical Officers (CMOs) collaborate directly with their peers in other regions and key medical stakeholders in order to share and provide important information about quality improvement initiatives. The CMS CMOs also participate in State and local programs, such as the Prescription Drug Monitoring Program. As CMOs present information on Affordable Care Act provisions, the importance of reducing ADEs and medication errors is emphasized. The CMS CMOs also emphasize the importance of being a meaningful user of EHRs as a means to reduce ADEs.

National Coverage Determinations^{xix}

CMS provides coverage to expedite the diagnosis of ADEs associated with anticoagulants and diabetes agents. Coverage policies for diagnostic testing for these ADEs and other indications are explained in detail within CMS National Coverage Determinations (NCDs).

Within the limits established by statute for Medicare benefits, five NCDs provide Medicare coverage for a variety of diagnostic tests for detecting, mitigating, and preventing ADEs in beneficiaries being treated with either anticoagulants or hypoglycemic agents.

^{xix} The list of all Medicare coverage determinations is available at: http://cms.hhs.gov/medicare-coverage-database/overview-and-quick-search.aspx?list_type=ncd

Two NCDs directly relate to detecting and preventing ADEs in patients receiving oral anticoagulants, like warfarin.

- NCD #190.11 provides for Medicare coverage for home prothrombin time (PT) testing, to help patients on warfarin test determine whether they may be out of therapeutic range. Home testing for PT/international normalized ratio (INR) decreases the risk of major hemorrhage and may improve warfarin compliance. This NCD was revised in 2008.
- NCD #90.1 provides for Medicare coverage under certain conditions for pharmacogenomic testing to inform physicians of gene variations that might increase or decrease a given patient's reaction to warfarin. Knowledge of the presence of gene variants may help predict the patient's ideal warfarin dose and lessen ADEs during the initial period of warfarin therapy. This NCD became available in 2009. Medicare (through the coverage with evidence development mechanism) is supporting ongoing clinical trials to determine this testing's actual benefit to patients.

Three NCDs directly relate to detection and prevention of ADEs in patients receiving diabetes agents, such as insulin.

- NCDs #40.1 and #40.2 provide Medicare coverage for home blood glucose monitoring (#40.2), as well as outpatient self-management training (#40.1). In combination, these NCDs provide a convenient way for patients with diabetes mellitus, working with their health care providers, to monitor blood glucose levels and achieve appropriate glucose control. Convenient and timely measurement of glucose levels can lead to adjustment of insulin dosage and help avoid the ADE of insufficient blood glucose.
- NCD #190.20 provides Medicare coverage for testing blood glucose levels in a clinical laboratory. Such testing confirms a patient's blood glucose level and may help physicians develop treatment plans for managing patients with abnormal glucose metabolism (e.g., as occurs with diabetes mellitus).

State Medicaid Drug Monitoring for ADEs in the Fee for Service Outpatient Pharmacy Program

Prescription drug coverage is an optional benefit under Federal Medicaid law; however, all States currently provide coverage for outpatient prescription drugs to most enrollees within their Medicaid programs. The Medicaid prescription drug programs include the management, development, and

administration of systems and data collection necessary to operate the Medicaid Drug Rebate program, the Federal Upper Limit calculation for multiple-source drugs, and the Drug Utilization Review (DUR) Program.

The Medicaid DUR Program^{xx} promotes patient safety through State-administered utilization management tools and processes. The State Medicaid agency's electronic monitoring system screens prescription drug claims to identify problems such as therapeutic duplication, drug-disease contraindications, incorrect dosage or duration of treatment, drug allergy, and clinical misuse or abuse in order to minimize or eliminate ADEs. DUR involves ongoing and periodic examination of claims data to identify patterns of medically unnecessary care and implements corrective action when needed.

Summary

This Incentives and Oversight section reviewed the existing incentives and oversight opportunities that encourage reductions in ADEs. As we move toward improved standardized measurement for ADEs, there may be opportunities to take advantage of these currently existing mechanisms to promote safer medication management.

^{xx} Detailed information on the Medicaid DUR program, along with reports the States submit annually on the operation of their programs, can be found at: <http://medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Drug-Utilization-Review.html>.

SECTION

5

Anticoagulants

Magnitude of the Problem

Anticoagulants are the mainstay of therapy for the acute and long-term prevention and treatment of numerous types of thromboembolic disorders. The prevention of thromboembolic stroke among patients with chronic atrial fibrillation (AF) is one of the primary indications for oral anticoagulation therapy. The current U.S. prevalence estimate of AF is approximately 2.6 million persons, and it is predicted to reach 12 million persons by the year 2050 [1]. In addition, anticoagulants are indicated in, and are increasingly prescribed for the prevention and treatment of, venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). It is estimated that more than 900,000 incident or recurrent, fatal and nonfatal VTE events occur in the United States annually [2]. Total annual direct medical costs and indirect costs (including lost earnings from premature mortality) of VTE are estimated to be \$13 to \$27 billion (USD 2011) [3]. Vitamin K antagonists (e.g., warfarin), unfractionated heparin (UFH, low-molecular-weight heparin [LMWH, e.g., enoxaparin and dalteparin]), direct thrombin inhibitors (e.g., argatroban and dabigatran), and factor Xa inhibitors (e.g., apixaban, fondaparinux, and rivaroxaban) are critical for the treatment and prevention of these disorders [4]. More than 30 million prescriptions for warfarin are written annually [5], more than two-thirds of Medicare beneficiaries with AF use warfarin [6], and total direct expenditures on warfarin have been estimated to be around \$158 million per quarter (USD 2010) [7]. Prescriptions of new oral anticoagulants (NOACs), such as dabigatran and rivaroxaban, are also increasing [7].

Bleeding is the primary ADE of concern associated with the use of anticoagulants [4, 5, 8, 9]. Thus, anticoagulation requires a careful balance between thrombotic and hemorrhagic risks and is easily influenced by a multitude of factors, such as patient age, co-morbidities, concomitant medications, and for warfarin especially, diet and pharmacogenetics. Bleeding rates associated with anticoagulants vary depending on the types of anticoagulant agents, dosing strategies, prophylactic versus therapeutic indications, durations of therapy, and patient populations. For warfarin, bleeding frequency has been estimated to be 15 percent to 20 percent per year, and life-threatening or fatal bleeding rates are

estimated at 1 percent to 3 percent per year [10]. Bleeding frequency while on warfarin is approximately five times that observed without warfarin therapy [11]. In recent clinical trials, NOACs (e.g., dabigatran and rivaroxaban) were associated with statistically significant lower rates of intracranial bleeding but higher rates of gastrointestinal bleeding relative to warfarin [12, 13, 14, 15]. Among patients with AF, studies indicate that NOACs were associated with statistically significant reductions in hemorrhagic strokes relative to warfarin [12, 13, 14, 15, 16]. In most studies to date of patients with VTE or PE, NOACs were associated with statistically significant reductions in major or clinically relevant bleeding, as compared with warfarin [17, 18, 19, 20, 21]. The bleeding risks associated with the use of NOACs outside of clinical trials and in populations who are especially vulnerable to ADEs (e.g., elderly patients and patients with renal impairment) require further postmarketing experience [22]. Data on the economic impact of anticoagulant-related harms are scarce. Among older adults (age \geq 65 years), a population shown to be especially vulnerable to ADEs, the annual cost of hospitalizations for warfarin-related bleeding has been estimated to be hundreds of millions of dollars [9, 23].

Among hospitalized patients (i.e., inpatient settings), significant challenges to optimal anticoagulation management persist despite advancements in health care delivery models and health information technology (health IT) resources (e.g., computerized physician order entry, electronic medication administration records, clinical decision support) [24, 25, 26, 27]. These challenges may result from clinicians having to rely on a wide range of anticoagulants with differing pharmacodynamic and pharmacokinetic profiles, the acuity and complexity of hospitalized patient populations, unique inpatient dosing considerations (e.g., rapidly changing renal function and extremes of weight), dietary inconsistency (e.g., changing or reduced dietary intake while hospitalized), the need for interruption of anticoagulation in preparation for invasive procedures, and transitions between parenterally and orally administered agents (e.g., in preparation for surgery or at time of hospital discharge). Care transitions from one unit to another (e.g., intensive care to step-down unit) and at discharge from the hospital to postacute or ambulatory care settings can also pose significant challenges to optimal anticoagulant management [28, 29].

Among nonhospitalized patients (i.e., outpatient settings), requirements for frequent monitoring, dose adjustments, and regular provider–patient contact can often render management of warfarin—the most commonly utilized oral anticoagulant in the outpatient setting [30]—labor-intensive and complex [31, 32]. However, patient interaction with coordinated anticoagulation management services [29, 33] and exposure to anticoagulant education [34] have been correlated with positive outcomes, as measured by

reductions in emergency department visits and hospitalizations and associated health care costs for thromboembolic and hemorrhagic events [35, 36, 37].

The introduction of NOACs to the market may attenuate some of the health care system burdens associated with outpatient warfarin management. The cost-effectiveness and postmarketing safety of these agents relative to warfarin is currently being evaluated [38, 39, 40]. Nevertheless, outpatient coordinated anticoagulation management services will likely continue to be heavily relied on to manage patient populations for whom NOACs are not prescribed. In addition, several of the critical elements of warfarin patient education will continue to be relevant for the NOACs, including such elements as patient recognition and understanding of signs and symptoms of thromboembolism/bleeding, appropriate dosing/administration instructions, and potential for drug-drug and drug-herbal interactions. Other important areas in which coordinated outpatient anticoagulation management may play a role for the NOACs are discussed below under the subheading “Evidence-Based Prevention Tools.”

Anticoagulants have been consistently identified as the most common causes of ADEs across health care settings.

Inpatient Settings

In a nationally representative sample of inpatient stays, anticoagulants caused an estimated 10 percent of drug-related adverse outcomes [41], and in a nationally representative sample of hospitalized Medicare beneficiaries, anticoagulants comprised one-third of identified ADEs (12 of 40 events) [42]. Data from inpatient settings suggest that anticoagulant ADEs most commonly result from medication errors, a large proportion are amenable to prevention, and they incur significant costs to the health care system, largely because of increased nursing and pharmacy costs [25, 27, 43, 44].

Outpatient Settings

On the basis of national public health surveillance data, anticoagulants have been shown to be among the most frequently implicated drug classes in ADEs that contribute to emergency department visits and hospital admissions [9, 45, 46, 47, 48, 49, 50]. Among older adults, warfarin was implicated in an estimated 17 percent of emergency department visits and 33 percent of emergent hospitalizations for ADEs annually [9, 50]. An estimated two-thirds of all warfarin-related emergent hospitalizations were because of unintentional overdose, as indicated by “warfarin overdose” in the clinician diagnosis, or supratherapeutic effects, as indicated by such factors as prolonged international normalized ratio (INR)

and/or hemorrhagic events [9]. Data for ADEs as causes of hospital readmissions are scarce; however, the few studies that are available also have found anticoagulant-related harms to be among the most common reasons for ADE-related readmissions [48, 51].

Long-Term Care (LTC) Settings

Data for anticoagulant-related harms in institutional LTC settings are more limited than for inpatient and other outpatient settings but also suggest that anticoagulant ADEs are common causes of preventable harms [52, 53]. As an example, it is estimated that there may be as many as 34,000 fatal, life-threatening, or serious warfarin-related ADEs per year in nursing home settings—many of which may be preventable [54]. In one cohort of nursing home residents, an estimated 29 percent of warfarin-related ADEs and 57 percent of serious, life-threatening, or fatal warfarin-related ADEs were deemed to be preventable [55]. In a retrospective cohort study within five VA nursing homes, even though INR-monitoring frequency was judged to be adequate, INRs were in therapeutic range for only 55 percent of the person-days, with a greater portion of person-time spent in the subtherapeutic (35 percent) compared with supratherapeutic range (11 percent) [56]. A similar study in LTC facilities found that residents spent only half of the time in therapeutic range, 36 percent of the time below the therapeutic range, and 13 percent of the time above therapeutic range [57].

Anticoagulation therapy is underutilized in the patient populations for whom it is most beneficial. Future public health initiatives will need to foster a comprehensive approach that addresses both anticoagulant effectiveness and safety.

AF, the most common arrhythmia encountered in clinical practice [58], is associated with a fourfold to fivefold increased risk of ischemic stroke. As an example of the importance of oral anticoagulation therapy in this patient population, warfarin has been shown to reduce the relative risk of ischemic stroke by approximately 64 percent and of death by approximately 25 percent [58]. The effectiveness of oral anticoagulation therapy for the prevention or treatment of VTE varies with indication; anticoagulation prophylaxis is associated with a 59 percent reduction in fatal pulmonary embolisms (PEs) and a 53 percent reduction in symptomatic DVT among acutely ill, hospitalized medical patients [59]. In medical patients at highest risk, anticoagulation reduces the risk of PE by approximately 40 percent to 60percent [60]. Warfarin reduces the risk of symptomatic VTE by approximately 80 percent among patients undergoing hip or knee arthroplasty or hip fracture surgery [60].

However, despite this well-established role for anticoagulation in prevention and treatment of thromboembolism, U.S. studies have consistently reported underuse of anticoagulants for these

indications [61, 62]. Underuse of anticoagulation when indicated can contribute to higher health care costs associated with strokes and VTE that otherwise would be prevented by effective anticoagulation therapy [63, 64]. In two studies involving a large, commercially insured patient population, less than one-half of high-risk stroke patients with AF received warfarin and more than three-quarters of high-risk VTE patients were considered noncompliant with warfarin therapy [65, 66]. A study conducted in a convenience sample of 21 community-based LTC facilities in a single State found that only 55 percent of ideal candidates for warfarin therapy were receiving it [57].

The factors underlying underuse of anticoagulants have not been explored extensively, but may include clinician and patient concerns regarding supratherapeutic INRs/bleeding risks [67] and lack of patient understanding of the importance of and indications for anticoagulation [68, 69]. Patients residing in rural or remote regions may especially be at increased risk of both undertreatment with anticoagulants and anticoagulant ADEs because of challenges in access to health care providers and anticoagulation management services. For example, studies have found that, despite having similar high-risk profiles, elderly, rural patients with chronic AF receive warfarin less frequently than urban patients [61, 70]. Providers caring for rural-dwelling patients may be reluctant to prescribe warfarin because of difficulties in followup and monitoring, which may contribute to underuse of anticoagulants in this population [61]. A better understanding of the extent of, and contributors to, undertreatment with anticoagulants is needed for those residing in rural areas and other patient populations who may be especially vulnerable to ADEs on the basis of race/ethnicity, socioeconomic status, educational attainment, low health literacy, physical disability, and physical distance from providers.

The ADE Action Plan is intended to address harms associated with exposure to anticoagulants; it does not address adverse events resulting from lack of treatment or undertreatment with anticoagulants (i.e., thromboembolic events, such as stroke or VTE). However, it is fully acknowledged that, in order to optimize health system and provider efforts in the area of anticoagulation management, future public health strategies will be needed to address both the effectiveness and safety of anticoagulation. Addressing the effectiveness of anticoagulation management requires a far more detailed approach than can be afforded by the ADE Action Plan alone. This includes considerations of effectiveness as it varies across indications for anticoagulation therapy (e.g., prophylactic vs. treatment indications) and consideration of the varying health system-, provider-, and patient-related factors that contribute to anticoagulant undertreatment. Differences in the ways providers may approach prescribing various anticoagulants (e.g., warfarin vs. NOACs) and a better understanding of the reasons underlying

suboptimal adherence by patients (e.g., differences in patient concerns regarding risk of stroke vs. perceived bleeding risks with anticoagulation) should also be considered. Surveillance resources that measure and track thromboembolic outcomes (e.g., stroke) and underlying indications (e.g., AF) need to be identified and explored for their strengths and limitations. Likewise, it will also be necessary to review evidence-based prevention strategies that specifically target use of anticoagulants in patients for whom they are most beneficial and that promote patient compliance/adherence. Although the ADE Action Plan does not directly address considerations that are specific to underuse of anticoagulants, it is hoped that aiming collective patient safety initiatives at better prevention of anticoagulant-related harms will foster health system-, provider-, and patient-level changes that will facilitate more confidence in anticoagulant therapy in the patient populations for whom it stands to be most beneficial.

Surveillance

Optimal use of anticoagulants requires accurate, timely, and adequately representative information on the “real-world” risks of bleeding complications.

Clinical trials evaluating the safety profile of various anticoagulants often exclude populations at highest risk of ADEs (e.g., older adults and patients with renal insufficiency). In addition, clinical trials are insufficiently powered to detect ADEs, have limited ability to examine drug-drug or drug-disease interactions that often contribute to ADEs in “real-world” settings, and include care processes that are not part of routine clinical practice [71]. For these reasons, postmarketing surveillance, like that currently conducted through various Federal systems, is crucial for estimating and characterizing the burden of anticoagulant-related harms in clinical practice or “real-world” settings.

Some Federal surveillance systems are currently capable of assessing the national scope of anticoagulant ADE burden. In addition, Federal Agencies involved in direct patient care (e.g., IHS, VHA) have the capacity to capture regional- and facility-level information on the quality of anticoagulant management. **Table 3** provides a summary of anticoagulant ADE-related metrics currently collected by Federal surveillance systems.

Table 3. Summary of Metrics Related to Anticoagulant ADEs Collected by Federal Surveillance Systems

Geographic Scope	Data Collection Methods	Anticoagulation Management or ADE Metrics: Inpatient Settings	Anticoagulation Management or ADE Metrics: Outpatient Settings
National ADE Incidence	Administrative claims and/or EHR data	AHRQ (NIS)* <ul style="list-style-type: none"> Inpatient stays with ICD-9-CM codes (964.2)* and E-codes (E934.2)* 	FDA (Sentinel Initiative, Mini-Sentinel):*** <ul style="list-style-type: none"> ED visits, hospitalizations for bleeding events and ADE signals (e.g., MI on dabigatran)
National ADE Incidence (+/-Rates)	Medical record review	AHRQ (MPSMS): ** <ul style="list-style-type: none"> Inpatient stays with combination of laboratory triggers and signs/symptoms in the medical record associated with UFH, LMWHs, or warfarin 	CDC (NEISS-CADES): <ul style="list-style-type: none"> ED visits, emergent hospitalizations for laboratory abnormalities (e.g., elevated INR), bleeding events, medication errors, and other ADEs relevant to anticoagulants diagnosed by treating clinician and documented in medical record narrative
National-, Regional-, and Facility-Level Spontaneous Reports	Voluntary reporting	DOD (Patient Safety Reporting System) <ul style="list-style-type: none"> Any clinician-diagnosed or patient-reported ADEs FDA (FAERS): <ul style="list-style-type: none"> Any clinician-diagnosed or patient-reported ADEs VA (VA ADERS): <ul style="list-style-type: none"> Any clinician-diagnosed or patient-reported ADEs 	DOD (Patient Safety Reporting System) <ul style="list-style-type: none"> Any clinician-diagnosed or patient-reported ADEs FDA (FAERS): <ul style="list-style-type: none"> Any clinician-diagnosed or patient-reported ADEs VA (VA ADERS): <ul style="list-style-type: none"> Any clinician-diagnosed or patient-reported ADEs
Regional-, Facility-Level ADE Incidence—Quality Improvement	Administrative claims and/or EHR data	VA: <ul style="list-style-type: none"> Anticoagulation process measures (e.g., out-of-range INR values, vitamin K orders, transfusions), ADEs (e.g., bleeding events) 	DOD (Pharmacovigilance Defense Application System): <ul style="list-style-type: none"> Outpatient clinic visits, ED visits, hospitalizations using relevant ICD-9-CM codes and/or CPT codes VA (VA Integrated Databases): <ul style="list-style-type: none"> Outpatient clinic visits, ED visits, hospitalizations using relevant ICD-9-CM codes and/or CPT codes for bleeding events, other relevant ADEs, and ADE signals (e.g., MI on dabigatran) BOP, IHS, VA: <ul style="list-style-type: none"> Anticoagulation process measures (e.g., TTR, out-of-range INR values, vitamin K orders, INR monitoring frequency)

*ICD-9-CM 964.2 refers to “Poisoning by anticoagulants” and E934.2 refers to “External Causes of Injury and Poisoning, Anticoagulants.”

**In 2015, the Medicare Patient Safety Monitoring System (MPSMS) will be replaced by the Quality and Safety Review System (QSRS). QSRs will aim to facilitate measurement of ADEs associated with additional types of anticoagulants.

***Currently, FDA Sentinel Initiative covers over 125 million lives; however, these do not constitute a nationally representative sample.

Abbreviations: ADE = adverse drug event; CPT = Current Procedural Terminology; E-code= external cause of injury code; ED = emergency department; EHR = electronic health record; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NIS = nationwide inpatient sample; TTR = time in therapeutic range; UFH = unfractionated heparin

Future Federal strategies will have to address challenges in capturing anticoagulant ADEs on the basis of surveillance data.

Although current Federal surveillance systems are capable of capturing an array of important outcomes reflective of anticoagulant ADEs, as well as process measures related to anticoagulant management, several challenges related to optimal surveillance of anticoagulant-related harms remain. Specifically, future Federal surveillance strategies will have to address challenges in capturing anticoagulant ADEs on the basis of validated diagnostic codes, using consistent definitions of bleeding, collecting data on ADEs occurring in settings that have otherwise been poorly studied (e.g., care transitions, nursing homes, home care), and monitoring ADEs associated with NOACs (for which well-established process measures are currently lacking). Opportunities to advance anticoagulant ADE surveillance strategies are summarized in **Figure 7**.

Figure 7. Federal Interagency Workgroup Recommendations for Actions That Can Potentially Advance Surveillance Strategies for Anticoagulant ADEs

Actions That Can Potentially Advance Surveillance Strategies for Anticoagulant ADEs

- **Address gaps in use of standard surveillance definitions for anticoagulant-related bleeding events in postmarketing and/or epidemiologic analyses.**
 - Better distinguish between major and minor anticoagulant-related bleeding events.
 - Minimize opportunities for bias or misclassification when characterizing bleeding events on the basis of retrospective medical review.
- **Assess the accuracy of diagnostic and procedural coding for capturing anticoagulant-related bleeding events.**
 - Assess specificity, sensitivity, PPV, and NPV of ICD and CPT codes for capturing anticoagulant-related bleeding events.
- **Improve availability of and access to integrated EHR data with linked pharmacy (medication exposure), laboratory, and outcomes (e.g., admission/discharge) data at national and local levels.**
- **Improve surveillance of anticoagulant ADEs resulting during care transitions, as well as those occurring in postacute care settings (e.g., nursing homes, home care) and among vulnerable patient populations (e.g., rural/remote-dwelling, low income, disabled patient populations).**
- **Address challenges in capturing anticoagulant ADEs among patients who seek care outside of integrated health care systems.**
- **Identify appropriate ADE surveillance metrics for NOACs and a long-term plan for ongoing monitoring of NOAC safety relative to warfarin in “real world” (nonclinical trial) settings.**

Abbreviations: ADE = adverse drug event; CPT = Current Procedural Terminology; EHR = electronic health record; ICD = International Classification of Diseases; NOAC = new oral anticoagulant; NPV = negative predictive value; PPV = positive predictive value

Monitoring anticoagulant ADEs on the basis of administrative claims data or population-based surveillance is challenging. First, ICD-9-CM codes, including External Causes of Injury codes (E-codes), have been commonly relied on to assess anticoagulant-related bleeding risks in postmarketing and epidemiologic studies [72, 73, 74]; however, very few studies have validated the accuracy of diagnostic and procedural codes in identifying the true frequency of anticoagulant-related bleeding events [75, 76, 77]. Second, the use of E-codes to capture anticoagulation-related bleeding is highly problematic because of the poor sensitivity of these types of codes for capturing ADEs, including anticoagulant ADEs [76]. Third, although definitions of major and minor bleeding in relation to anticoagulants have been universally agreed on for some time [78], these definitions are not consistently applied across postmarketing and epidemiologic studies, rendering comparisons of studies somewhat challenging [78]. Fourth, NOACs present a unique challenge to anticoagulant ADE surveillance in that they currently lack well-established process measures (e.g., laboratory coagulation markers) to facilitate adequate monitoring of harms [22]. Few surveillance systems are able to provide robust information regarding anticoagulant ADEs occurring as a result of care transitions issues [79], or occurring in nursing home or home care settings, and there are insufficient data on anticoagulant ADEs resulting in hospital readmissions. Integrated health care data that allow linking of exposure (e.g., anticoagulant prescription) and outcome variables (e.g., subsequent emergency department visit or hospitalization for bleeding event) across care settings will be important for furthering the understanding of the burden and impact of anticoagulant ADEs across care transitions, as well as for implementing and assessing prevention efforts across the patient care spectrum [80].

Evidence-Based Prevention Tools

Evidence-based guidelines and prevention strategies/tools that aim to carefully balance the thromboembolic and hemorrhagic risks associated with anticoagulants are available [4]. However, given the complex and rapidly evolving nature of the field of antithrombotic management, opportunities for advancement in the area of prevention remain. Although it is acknowledged that there is a subset of especially high-risk anticoagulated patients for whom bleeding cannot be prevented despite optimal care, there remains a large proportion of anticoagulant ADEs that may be amenable to prevention, particularly in outpatient settings [9, 81]. A summary of existing Federal prevention strategies/tools that address safe and effective management of anticoagulation therapy are summarized in **Figure 8**.

Figure 8. Federal Assets Related to Safe Management of Anticoagulation Therapy, as Identified by the National Quality Strategy Priorities

<p style="text-align: center;"><u>Resources for Safer Care—Health Care Provider Knowledge</u></p> <ul style="list-style-type: none"> ▪ BOP: <ul style="list-style-type: none"> – Anticoagulation Protocol (for warfarin, heparin, NOACs)—Includes dosing algorithms, guidelines to manage high INR values, guidelines to manage anticoagulation therapy in patients requiring invasive procedures, and bridge therapy protocols ▪ IHS: <ul style="list-style-type: none"> – National Anticoagulation Training Program—3-day certificate training program providing specialized training in anticoagulation and disease management; other Federal partners (BOP, DOD, VA) also participate ▪ VA: <ul style="list-style-type: none"> – Educational opportunities for health care providers include anticoagulation-related cases for grand rounds and teaching cases for medical, nursing, and pharmacy staff; Web-based education courses (e.g., self-learning modules, live broadcasts on anticoagulation management, and CE programs on anticoagulation safety)
<p style="text-align: center;"><u>Resources for Patient and Family Engagement</u></p> <ul style="list-style-type: none"> ▪ ACL: <ul style="list-style-type: none"> – Community organizations offer programs that have been or are currently supported, in part, by Federal funds, such as <ol style="list-style-type: none"> 1. Stanford Chronic Disease Self-Management Program—6-week program to help participants better manage their medications, including information about anticoagulants 2. HomeMedsSM Medication Management System—Multidisciplinary collaborative providing patient counseling, reassessment, and adjustment of medication regimens for older adults in various nonacute health care settings (e.g., home care) ▪ AHRQ: <ul style="list-style-type: none"> – Patient education information sheet (“Blood Thinner Pills: Your Guide to Using Them Safely”) & video ▪ FDA: <ul style="list-style-type: none"> – Medication guides (e.g., available for apixaban, dabigatran, rivaroxaban, and warfarin)
<p style="text-align: center;"><u>Resources for Communication and Coordination of Care</u></p> <ul style="list-style-type: none"> ▪ AHRQ: <ul style="list-style-type: none"> – Project RED—Includes a number of medication-related strategies (e.g., active medication reconciliation, medication teaching for patients and caregivers, development of medication list for patients and their health care providers) ▪ BOP, IHS: <ul style="list-style-type: none"> – Anticoagulation Management Electronic Flowsheet—Integrates laboratory and pharmacy data in one location, in an easily accessible format, in close to real time ▪ VA: <ul style="list-style-type: none"> – Traveling Veterans Directory—Addresses challenges associated with care coordination for Veterans seeking care at different VA medical facilities when traveling – Anticoagulation Management Tool—Designed to simplify the complex, time-consuming processes required to manage outpatient anticoagulant medications and allows health care providers to enter outside laboratory results, review laboratory data, record activities on an anticoagulation flowsheet; creates a loss to followup list; calculates TTR; and develops complications reports – Electronic consults and templates—Coordinates care with outpatient anticoagulation clinics on discharge

Figure 8. Federal Assets Related to Safe Management of Anticoagulation Therapy, as Identified by the National Quality Strategy Priorities (continued)

<p style="text-align: center;"><u>Resources for Science-driven Prevention and Treatment</u></p> <ul style="list-style-type: none"> ▪ BOP, DOD, IHS, VA: <ul style="list-style-type: none"> – Systematic and coordinated anticoagulation management models of care (e.g., anticoagulation clinics, support for warfarin PST/PSM) ▪ VA: <ul style="list-style-type: none"> – Medication Use Evaluation Tracker (MUET)—Available for dabigatran and rivaroxaban to identify and intervene on inappropriate use and prevent potential ADEs – Electronic Clinical Decision Support templates—For ordering and monitoring NOACs
<p style="text-align: center;"><u>Resources to Promote Best Practices within Communities</u></p> <ul style="list-style-type: none"> ▪ VA: <ul style="list-style-type: none"> – Shared Resource Center—Lists strong clinical practices, tools, and patient education materials related to anticoagulation management

Abbreviations: ADE = adverse drug event; INR = international normalized ratio; NOAC = new oral anticoagulant; PSM = patient self-Monitoring; PST = patient self-testing; TTR = time in therapeutic range

Inpatient Settings

Compared with other medications, anticoagulants are more likely to cause harm to hospitalized patients because of a variety of factors, including complex dosing, the need for frequent monitoring, and transitions between parenterally and orally administered agents (e.g., in preparation for surgery or at time of hospital discharge). Goals and strategies for improving anticoagulation management in inpatient settings have been identified. For example, The Joint Commission (TJC) has identified the National Patient Safety Goal (NPSG) 03.05.01: “Reduce the likelihood of patient harm associated with the use of anticoagulant therapy,” which includes the performance element: “Evaluate anticoagulation safety practices, take action to improve practices, and measure the effectiveness of those actions in a time frame determined by the organization” [82]. Care processes that meet these goals may include use of approved protocols for the initiation and maintenance of anticoagulant therapy; use of programmable pumps for UFH therapy; implementation of policies that address baseline and ongoing laboratory monitoring for anticoagulants; and education regarding anticoagulant therapy for prescribers, staff, patients, and families [82].

The Institute for Safe Medication Practices (ISMP) “Pathways for Medication Safety” toolkit describes a comprehensive set of tools to help hospitals adopt a “process-driven, systems-based” approach to reduce medication errors and improve patient care [83]. Systematic processes to facilitate inpatient anticoagulation safety can include such strategies as use of standardized anticoagulation dosing protocols when appropriate, implementation of technology (e.g., computerized physician order entry,

bar code scanning, programmable infusion pumps, and dose range checking), human or computer-based alert systems, and multidisciplinary approaches to anticoagulation management [30].

The National Quality Forum (NQF), which works to identify and achieve consensus on national health care quality measures, has also endorsed a patient safety goal for reducing anticoagulant-related harms through Safe Practice #29 (Anticoagulation Therapy): “Organizations should implement practices to prevent patient harm due to anticoagulant therapy” [84].

Goals such as those set by TJC, NQF, and ISMP suggest that multidisciplinary, coordinated, and systematic processes will be critical in facilitating reductions in anticoagulant ADEs among hospitalized patients [29, 82, 83, 84]. Challenges that will need to be addressed to reduce inpatient anticoagulant ADEs may include

- Consideration of the acuity and complexity of the hospitalized patient population and the need for individualized treatments (relative to outpatient settings)
- Lack of a nationally recognized, widely shared, comprehensive set of best practices or standards focusing specifically on safe use of anticoagulants in hospitalized patient populations
- Need for multifaceted interventions to deliver high-quality anticoagulation management
- Difficulty in translating clinical guidelines into ready-to-use inpatient health care quality metrics (i.e., high-quality anticoagulation “process” measures are not as easily measured in inpatient relative to outpatient settings)

Opportunities for advancing anticoagulant ADE prevention strategies/tools in inpatient settings, as identified by the NQS Priorities, are summarized in **Figure 9** and discussed further below.

Figure 9. Opportunities for Advancing Anticoagulant ADE Prevention Strategies/Tools, as Identified by the National Quality Strategy Priorities—Inpatient Settings

<p style="text-align: center;">Safer Care</p>	<ul style="list-style-type: none"> ▪ Improve provider knowledge of high-quality inpatient anticoagulation management through provider education ▪ Improve dissemination of/increase accessibility to evidence-based, high-quality inpatient anticoagulation management strategies/tools ▪ Address gaps in evidence and provider knowledge with regard to management of NOACs through development of guidelines/algorithms for safe use (e.g., clinician guidance for laboratory testing)
<p style="text-align: center;">Effective Communication and Coordination of Care</p>	<ul style="list-style-type: none"> ▪ Improve EHR tools to enable provider access to real-time, integrated, linked pharmacy-laboratory data to facilitate seamless access to pertinent medication and laboratory results, for example, <ul style="list-style-type: none"> – Support development of electronic flowsheets that display trends in daily labs, concomitant medications, reversal medications, etc., that are specific to and can support optimal anticoagulation management – Support development of clinical decision support tools specific to anticoagulation management ▪ Better integrate anticoagulation-specific targets into currently existing care transition models
<p style="text-align: center;">Science-Driven Prevention and Treatment</p>	<ul style="list-style-type: none"> ▪ Promote a multidisciplinary, coordinated, and systematic approach to inpatient anticoagulation management; for example, <ul style="list-style-type: none"> – “Anticoagulation rounds”, pharmacist-/nurse-managed anticoagulation services, “Anticoagulation Stewardship.” – “culture of safety” in anticoagulation management ▪ Better address safe use of anticoagulants commonly utilized in inpatient settings (e.g., heparin) and NOACs in nationally recognized health care quality/patient safety measures and in nationally recognized clinical guidelines

Promotion of Best Practices Within Communities

- Identify and promote adoption of standards that constitute high-quality anticoagulation management (e.g., “Anticoagulation Center of Excellence”)
- Improve dissemination and sharing of strategies and results from large-scale, quality-improvement learning initiatives targeting anticoagulant ADE prevention among health care systems/facilities

Abbreviations: ADE = adverse drug event; EHR = electronic health record; NOAC = new oral anticoagulant

Gaps remain in the availability and successful dissemination of evidence-based strategies for optimizing inpatient anticoagulation management.

Despite widespread recognition of the important contribution of anticoagulants to preventable harm in inpatient settings, there remain key areas in which use of these agents could be optimized among hospitalized patients. These include: (1) wider development and dissemination of inpatient-specific anticoagulation management guidelines, (2) standardization of key coagulation parameters across laboratory systems, and (3) improvement of anticoagulation-related training and education of inpatient providers. Although standardized dosing protocols have a role in promoting effective and safe dosing of certain anticoagulants in inpatient settings [30], these cannot be relied on exclusively, as anticoagulant management in hospitalized patients requires more extensive considerations than can be afforded by dosing protocols alone (e.g., emergently holding and restarting anticoagulation and managing bleeding or reversing anticoagulation). Development and dissemination of institutional guidelines that are evidence based, evaluated, and revised as necessary, and that leverage multidisciplinary teams may be important in that regard [28, 29]. Mechanisms that Federal partners could leverage to facilitate spreading best practices across facilities should also be explored. In addition, to the extent that clinical laboratory approaches/assays are known to differ among institutions [85], there appears to be an important need to identify the role that Federal Agencies could play in promoting standardization of key coagulation parameters across laboratories (e.g., achieving alignment in Activated Partial Thrombosis Time [aPTT] and antifactor Xa assays across hospital laboratories). Further, the introduction of the NOACs to the market requires that tools be developed to ensure that clinical laboratories and providers are equipped and educated regarding appropriate use of laboratory tests with these agents. Anticoagulation training programs may need to be expanded to better target educational needs of inpatient anticoagulation providers, who have to take into account unique considerations when managing anticoagulation for acute or critically ill patients. Below is further discussion of these and other areas in which Federal Agencies could play an important role in advancing evidence-based prevention strategies targeted at minimizing anticoagulant ADEs.

Federal Agencies should play a role in advancing health IT–based strategies, including EHR standards, to further inpatient anticoagulant ADE prevention.

The acuity and complexity of the hospitalized patient population requires that providers have access to real-time, integrated, linked pharmacy–laboratory data to facilitate seamless access to pertinent medication and laboratory data, and deliver optimal inpatient anticoagulation management [29]. Processes and tools for inpatient anticoagulation management should be integrated with the EHR to facilitate accurate and efficient communication of clinical and laboratory information pertinent to inpatient anticoagulation management. Integration of pharmacy order entry systems with laboratory reporting systems will support the timely review of key laboratory values prior to ordering, dispensing, or administering anticoagulants. Examples might include tools such as an electronic anticoagulation management flowsheet that displays trends in such metrics as daily labs, concomitant medications, and reversal medications specific to anticoagulation management. Regardless of the health IT-based approaches taken to optimize safety of inpatient anticoagulation delivery, innovative health IT in this area should be prioritized on the basis of evidence; be tested in collaboration with facilities and providers; function efficiently in current workflow; and deliver accurate, timely, and clinically relevant content [86]. Unintended consequences of any new health IT-based approaches to care should also be taken into consideration prior to implementation.

Federal Agencies that provide direct patient care play an important role in advancing evidence-based strategies for anticoagulant ADE prevention.

Currently, evidence-based guidelines or tools that address high-quality anticoagulation management in inpatient settings exist primarily at the level of a single health system or facility. Some organizations, such as the Anticoagulation Forum—a nonprofit, multidisciplinary organization with a goal of improving quality of care among patients taking antithrombotic medications—are leading strategies that foster dissemination of best practices and prevention strategies across health care systems and facilities [87]. However, there remains tremendous opportunity to learn about high-quality facility strategies and tools from Federal partners that provide direct patient care (e.g., BOP, DOD, HRSA, IHS, and VA). One such example from the VA National Center for Patient Safety is summarized in **Table 4**.

Table 4. Department of Veterans Affairs—National Center for Patient Safety “Actions From VA and Non-VA Facilities To Control Vulnerability” From Anticoagulation

System	Action
Storage	<ul style="list-style-type: none"> ▪ Limit the availability of anticoagulant drugs from floor stock to reduce misadministration.
Ordering	<ul style="list-style-type: none"> ▪ Establish weight-based heparin protocols (to improve consistency) with education on exclusion and inclusion criteria. Closely monitor for success and failures and adjustment of protocols, as necessary.
Preparation	<ul style="list-style-type: none"> ▪ Standardize one size/concentration of IV bags for continuous IV heparin, using an even number of units per mL [e.g., 50 units per mL] to simplify calculations. ▪ Limit the size of the infusion bag of heparin to reduce risk if free flow or overinfusions occur (250 mL vs. 500 mL). ▪ Provide heparin in dosage forms that are as close as possible to what is ordered (e.g., 5,000-unit or 10,000-unit vials for bolus use).
Distribution	<ul style="list-style-type: none"> ▪ Use manufacturer’s premade solutions to reduce compounding and labeling errors.
Administration	<ul style="list-style-type: none"> ▪ Establish a food and drug interaction program/policy that addresses enteral feedings and warfarin administration. ▪ Establish double-check systems to verify correct pump settings and calculations. ▪ Enforce review of order before drug administration. ▪ Include drip charts on the infusion bags to improve the ability to adjust rates without mathematical errors.
Therapeutic Management	<ul style="list-style-type: none"> ▪ Establish a pharmacy-based inpatient anticoagulation service to improve monitoring, followup, and transitioning to warfarin. ▪ Standardize the monitoring of anticoagulant laboratory work so that clinical changes are detected early (e.g., hemoglobin, platelets).

Source: U.S. Department of Veterans Affairs—National Center for Patient Safety. (2012, December 13). Anticoagulation Vulnerability. Available at: <http://www.patientsafety.va.gov/professionals/hazards/anticoag.asp>.

Federal Agencies should support the dissemination and uptake of evidence-based strategies for anticoagulant ADE prevention across health care systems and facilities.

The Centers for Medicare & Medicaid Services’ (CMS) Center for Medicare & Medicaid Innovation (CMMI)–led Partnership for Patients Initiative serves as an example of the way Federal funding could enhance private sector efforts to prevent anticoagulant ADEs and facilitate the sharing of evidence-based prevention strategies across facilities. The goals of the Partnership for Patients Initiative are to make care safer by reducing hospital-acquired conditions and improve care transitions by decreasing preventable complications during transitions from one health care setting to another. Since 2011, the Partnership for Patients initiative has supported large networks of health systems and hospitals (Hospital Engagement Networks [HENS]) across the country by providing strategies aimed at monitoring safe use of warfarin in inpatient settings [88, 89]. Example metrics related to inpatient anticoagulation management include

- INR >5 per 1,000 patient days
- Percentage of patients on warfarin with INR outside threshold

- Anticoagulant ADE per 1,000 patient days
- Percentage of patients on warfarin receiving warfarin education
- Percentage of patients on warfarin who have dose management protocols
- Percentage of patients on heparin dosing protocol
- Percentage of acute care inpatients on warfarin and/or heparin with evidence of an INR or aPTT performed during the hospitalization

As of May 2013, there were more than 650 hospitals participating in the Partnership for Patients Initiative with at least 6 months of data related to inpatient warfarin safety. Mechanisms such as those employed by the HENs to rapidly disseminate information about successful quality improvement initiatives may be helpful in spreading best practices across facilities and in preventing adoption of ineffective strategies.

Federal partners should lead efforts to promote the concept of “anticoagulation stewardship” to reduce anticoagulant ADE burden.

Not all health care facilities may be able to rely primarily on health IT-based systems to improve inpatient anticoagulation management. Consequently, Federal Agencies could support other multidisciplinary and systematic approaches to anticoagulation management at the health system level. Such strategies may include nurse- or pharmacist-managed inpatient anticoagulation services and “multidisciplinary anticoagulation rounds” that include representatives from medicine, pharmacy, nursing, and patient safety [90, 91, 92, 93]. In addition, promoting the concept of “anticoagulation stewardship” may contribute to promotion of a culture of safety specifically around anticoagulants [94, 95, 96]. The concept of anticoagulation stewardship refers to a multidisciplinary, coordinated, and systematic approach to care. This is analogous to the successful approach used to improve antibiotic use in inpatient settings [97]. As with efforts to implement successful and sustainable antibiotic stewardship programs, anticoagulation stewardship will likely require a commitment from health system leadership, including support in the form of funding and resources, engagement of a key health care provider who can champion anticoagulation stewardship efforts, and identification of methods and key metrics by which to continuously assess outcomes associated with such efforts [97].

Outpatient Settings

Although prescribing of NOACs is increasing, recent data available (2011) suggest that warfarin remains the most commonly utilized oral anticoagulant in outpatient settings [7, 30]. Nationally recognized clinical guidelines from the American College of Chest Physicians (ACCP) recommend that health care

providers who manage oral anticoagulation therapy do so in a “systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, followup, and good patient communication of results and dosing decisions” [4]. Systematic and coordinated anticoagulation care is usually defined as a specialized program of patient management that focuses exclusively on managing oral anticoagulation therapy. This differs from routine medical care, in which a patient’s own physician or a variety of physicians provides care without systematic coordination. Features of such services generally include

- A program directed by a single physician whose primary responsibility revolves around oversight of oral anticoagulation management services
- Delivery of care by pharmacists, registered nurses, nurse practitioners, or physician assistants following a physician-approved protocol
- Centralized management of a population of patients with direction provided by different primary or referring physicians for individual patients [98].

Federal Agencies that provide direct patient care should continue to explore opportunities to improve uptake of evidence-based, systematic, and coordinated models of anticoagulation management.

In outpatient hospital departments and in the community, anticoagulation clinics (or “Coumadin clinics”) are the settings that most often deliver systematic and coordinated oral anticoagulation management. In the United States, it is estimated that there are approximately 3,000 such anticoagulation clinics [99]. The VA has long embraced the model of anticoagulation clinic services. In an internal survey conducted in 2008, more than 95 percent of VA medical facilities were identified as having specialized outpatient anticoagulation management (including anticoagulation clinics) [100].

There is a large and longstanding body of evidence which indicates that anticoagulation clinic services are associated with improved anticoagulation management relative to “usual medical care,” as reflected by such measures as higher time in therapeutic range (TTR), higher proportion of INR values within target ranges, and reductions in emergency department visits and hospital admissions for thromboembolic and hemorrhagic outcomes (including major and fatal bleeding episodes) [37, 101, 102]. Anticoagulation clinics have also demonstrated reductions in health care costs by \$800 to \$1,600 per patient per year [98, 103]. Research results suggest that health systems could expand the use of anticoagulation clinics and still save money [104]. Despite this evidence, it is estimated that only 30 percent to 40percent of U.S. patients receiving oral anticoagulation therapy are enrolled in such clinics

[99]. Barriers to wider enrollment in anticoagulation clinics range from provider-related factors (e.g., fear of loss of autonomy in providing anticoagulation care), patient-related factors (e.g., lack of physical proximity to such services for rural/remote patient populations), systems-related factors (e.g., concerns regarding benefits of such services combined with implementation costs, training of staff), and economic factors (e.g., challenges in payment/coverage for these services).

The barriers that are most likely amenable to being addressed by Federal Agencies are those related to provider/patient education and economic barriers. Provider education programs such as the National Anticoagulation Training Program coordinated by IHS (in which BOP, DOD, and VA facilities also participate) may serve as a model of a systematic approach to deliver education around optimal anticoagulation management. Public-private partnerships with organizations such as the Anticoagulation Forum, which also is facilitating widely and easily accessible formats for provider education aimed at improving the quality of anticoagulation care, could also be considered. Potential opportunities for overcoming economic barriers related to wider uptake of anticoagulation clinic services are discussed further below under the subheading “Incentives and Oversight.”

It is important to note that establishing an anticoagulation clinic is only the first step toward reducing anticoagulation ADEs. Larger challenges remain, including ensuring that patients are referred to, or utilize, such clinics and optimizing communication among providers caring for the same patient within and outside these clinics. This is especially true for patients who do not regularly seek care in integrated health care systems and for rural/remote populations. Barriers to physically accessing clinics may also exist for older adults, regardless of where they reside, because of such factors as having limited mobility, being home bound, and having cognitive impairment [105].

Even for those with access to anticoagulation clinic services, challenges surrounding their effective use remain, including recognition that some patients are at especially high risk for bleeding despite the use of systematic and coordinated models of anticoagulation management. In addition, some patients may not be appropriate candidates for such services (e.g., rural/remote patients or patients with poor adherence to scheduled visits). Finally, use of anticoagulation clinic services may be more effective for the prevention of thromboembolic events than for prevention of hemorrhagic events [35, 101, 102, 106]. Nevertheless, studies of anticoagulation clinic services have generally demonstrated positive, substantial impacts on all fronts of anticoagulation management, including effectiveness, safety, and costs.

Because of some of these limitations of anticoagulation clinic services, alternative models of oral anticoagulation management have also been adopted [107, 108, 109]. Patient self-testing (PST) of INR and patient adjustment of their anticoagulant dose (patient self-management, or PSM) have proved to be effective strategies for improving warfarin effectiveness and safety outcomes [4]. However, current nationally recognized clinical guidelines recommend that these modalities be limited to patients who are “motivated and can demonstrate competency in self-management strategies, including the self-testing equipment” [4]. As with anticoagulation clinic services, there is a need to facilitate better identification of patients who are appropriate candidates for PST/PSM models of care and to improve uptake of such models of care for those patients when appropriate. For patients residing in rural/remote areas, increasing access to pharmacist services and telephone-based management may be effective strategies to assist general practitioners in the management of their anticoagulated patients [101, 107, 108].

Although the introduction of NOACs will shift some use away from warfarin, it is likely that coordinated anticoagulation management services will continue to play an important role in the care of patients receiving NOACs. Anticoagulation clinic services may evolve into areas such as: identifying appropriate patient candidates for these new agents, transitioning safely among older and newer agents, monitoring patients during interruption of therapy (e.g., periprocedural period), ensuring accurate age-dependent and/or renal function-dependent dose adjustments, helping to define the use and interpretation of potential laboratory coagulation parameters (e.g., thrombin time and antifactor Xa), providing patient education (e.g., counseling patients on the importance of adherence because of the shorter half-lives of the newer agents relative to warfarin and the increased risk of thrombosis during interruptions of therapy), and general coordination and communication of anticoagulation management issues among a patient’s multiple providers [79].

In addition, several of the critical elements of warfarin patient education will continue to be relevant for the NOACs. These elements include patient recognition and understanding of signs and symptoms of bleeding/stroke, appropriate dosing/administration instructions, and education on the potential for drug–drug and drug–herbal interactions. As these agents become more widely prescribed, evidence-based prevention strategies/tools that better address the safe use of NOACs will need to be developed. Specific areas in which such tools could be targeted are discussed below under the subheading “Research (Unanswered Questions).” Opportunities for advancing anticoagulant ADE prevention strategies/tools in outpatient settings for both warfarin and NOACs, as identified by the NQS Priorities, are summarized in **Figure 10**.

Figure 10. Opportunities for Advancing Anticoagulant ADE Prevention Strategies/Tools, as Identified by the National Quality Strategy Priorities—Outpatient Settings

<p>Safer Care</p>	<ul style="list-style-type: none"> ▪ Improve provider knowledge of high-quality outpatient anticoagulation management through provider education ▪ Improve uptake of evidence-based anticoagulation management models, including anticoagulation clinic services and warfarin PST/PSM ▪ Address provider concerns around supratherapeutic INRs and resultant undertreatment ▪ Address gaps in evidence and provider knowledge with regard to management of NOACs through development of guidelines/algorithms for safe use (including clinician guidance on laboratory testing)
<p>Patient and Family Engagement</p>	<ul style="list-style-type: none"> ▪ Improve incorporation of anticoagulation-specific patient management into chronic disease education programs and other patient education/health literacy tools
<p>Effective Communication and Coordination of Care</p>	<ul style="list-style-type: none"> ▪ Better integrate anticoagulation-specific targets into currently existing care transition models
<p>Science-Driven Prevention and Treatment</p>	<ul style="list-style-type: none"> ▪ Address factors that contribute to interfacility variability in anticoagulation services (including outpatient clinic services) ▪ Better address safe use of NOACs in national health care quality/patient safety measures and nationally recognized clinical guidelines ▪ Address gaps in guidelines to identify patients at high risk for bleeding events (e.g., effectiveness of bleeding scores in relation to NOACs)
<p>Promotion of Best Practices Within Communities</p>	<ul style="list-style-type: none"> ▪ Identify and promote adoption of standards that constitute high-quality anticoagulation management (e.g., “Anticoagulation Center of Excellence”) ▪ Improve dissemination and sharing of strategies and results from large-scale, quality-improvement learning initiatives targeting anticoagulant ADE prevention among health care systems/facilities

Abbreviations: INR = international normalized ratio; NOAC = new oral anticoagulant; PSM = patient self-management; PST = patient self-testing

Note About Use of Pharmacogenomics-Guided Dosing To Optimize Warfarin Safety

Genetic variations are among the most important determinants of variability in warfarin dosing requirements [110]. For this reason, pharmacogenomic testing has been a longstanding research area of interest for optimization of warfarin safety and effectiveness. Dosing algorithms that incorporate pharmacogenomic considerations (e.g., <http://www.warfarindosing.org>) have been explored for their comparative effectiveness, their relative utility among different populations (e.g., Black vs. non-Black patients), and their impact on such end points as percentage of out-of-range INRs and time in therapeutic range [111, 112, 113, 114]. However, challenges in integrating pharmacogenomics into clinical practice have hindered uptake of pharmacogenomics-guided warfarin management [115]. For example, many medical centers currently do not have warfarin pharmacogenomics testing capabilities and thus rely on outsourcing to clinical laboratories with long turnaround times for results [116, 117]. In addition, the cost of pharmacogenetic testing is generally not reimbursed by public and private insurance plans [116, 117]. Finally, the integration of pharmacogenomics data with clinical decision support software to guide therapy has not been fully realized [115]. Most recently, data from the largest pharmacogenomics clinical trial in the U.S. population to date indicate that genotype-guided warfarin dosing strategies do not affect anticoagulation control, as measured by time in therapeutic range, time to achievement of first INR, time to stable INR dose, or a composite safety end point of overcoagulation and undercoagulation (time to any INR of ≥ 4 , major bleeding episodes, or thromboembolism) [118]. Given the challenges and limitations associated with pharmacogenomics-guided warfarin management seen to date, it will be important to focus future public health efforts on supporting other strategies, such as improving clinicians' ability to select the most appropriate anticoagulant agents for their patients; facilitating patient access to the most appropriate anticoagulation management modality; bolstering laboratory standards and communication infrastructure around key coagulation parameters; and supporting improved communication among laboratories, providers, and patients [110].

Federal Agencies should explore ways to better incorporate effective anticoagulation ADE prevention strategies in long-term care and care transitions settings.

Long-term Care (LTC) Settings

More needs to be learned about the quality and outcomes associated with anticoagulation therapy in institutional and noninstitutional LTC settings, including the extent of adoption and application of best practices for anticoagulant ADE prevention [119]. Barriers to providing high-quality anticoagulation

management in LTC settings have not been thoroughly studied; however, in nursing homes, these may include provider concerns around supratherapeutic INRs and resultant undertreatment of nursing home residents, provider fear of loss of professional autonomy in anticoagulation management through use of dosing nomograms or guidelines, and costs of implementing dosing support tools/resources (e.g., nomograms, clinical decision support software). In LTC settings such as nursing homes, there may be a need to better address risks/benefits associated with point-of-care (POC) INR monitoring versus venipuncture, dosing practices, rates of achieving appropriate INR and TTR goals, management strategies for elevated INRs or bleeding events, and overall quality assurance processes associated with nursing home anticoagulation management. Communication challenges may be one of the foremost barriers to delivering optimal anticoagulation management in LTC settings. Limited accessibility to EHRs outside a particular facility and the challenge of transmitting pertinent anticoagulation-related data elements in an efficient manner to a remote provider that can manage patients' anticoagulation may complicate anticoagulation services in LTC settings. Strategies aimed at improving anticoagulation safety and providing high-quality anticoagulation management in LTC settings may include

- Standardizing anticoagulation management treatment approaches across LTC settings, which may include facilitating and promoting uptake of currently available guidelines, such as American Medical Directors Association (AMDA) Antithrombotic Therapy in the Long-Term Care Setting guidelines [119], or developing LTC-specific anticoagulation management tools/resources (e.g., EHR-based clinical decision support tools)
- Determining reimbursement barriers to POC INR testing, as well as to management/oversight responsibilities for anticoagulation services
- Providing strategies for facility-based active and ongoing surveillance of anticoagulation safety-related metrics, including ones targeting adequate monitoring transitions to or therapy with NOACs
- Improving use of anticoagulant ADE prevention strategies/tools (e.g., dosing nomograms, clinical decision support, facility policies/guidelines, and preprinted medication orders that identify patient specific goals/target INR ranges)
- Identifying a single anticoagulation provider (e.g., nurse practitioner, consultant pharmacist, anticoagulation clinic pharmacist) who takes primary responsibility for anticoagulation management

In home care settings, provision of in-home laboratory services is limited by reimbursement challenges; this can contribute to inadequate monitoring of postacute patients discharged to these settings.

Changes in reimbursement policy for the use of portable INR devices in home care settings may allow for more frequent laboratory monitoring to prevent possible complications from anticoagulation therapy in these settings. Alternatively, adequate staff training in skills required to perform in-home laboratory draws may improve the validity of laboratory results obtained in these settings. In addition, significant lag time in reporting laboratory results to laboratory portals for nurses or consultant pharmacists to review may result in delayed action taken for anticoagulation management. For this reason, there may be a need for more centralized EHR tools that promote data exchange and facilitate provider access to real-time, linked pharmacy–laboratory data. Finally, limits on prescribing privileges for nurse practitioners resulting from requirements, such as physician approval of recommendations or patient encounter prior to physician approval, may limit more efficient and timely anticoagulation management in home care settings.

Care Transitions

Inpatient and ambulatory anticoagulation management services are an essential component of care transitions. Although several care transitions models have been developed with the goal of improving the hospital discharge process and reducing readmission rates, few address issues of care transitions into, within, and out of the hospital that are specific to anticoagulation management [79]. Anticoagulated patients will likely remain at high risk for ADEs as long as there remain suboptimal systems for communication between inpatient and outpatient providers, limited ability to access medication lists and laboratory results for patients who are managed outside of integrated health care systems, and limits in capability of disparate EHRs to exchange pertinent information.

Strategies targeted at improving care transitions for anticoagulated patients have not been thoroughly studied. However, in one study, when inpatient pharmacist-directed anticoagulation services were involved in providing warfarin dosing and monitoring, as well as the coordination of care from inpatient to outpatient settings, improvements were seen in care transition metrics, including enrollment in outpatient anticoagulation clinics, documented inpatient-to-outpatient provider contact, documented inpatient provider-to-anticoagulation clinic communication, and patient followup within 5 days of hospital discharge [93]. Patient education, a core tenet of care transition models, may also play a key role in anticoagulant ADE prevention during care transitions. Patient education is a critical component of safe care transitions [79], and it plays an important role in preventing anticoagulant ADEs. Patient education about warfarin therapy has been associated with stability of therapy, as measured by TTR [120] and reductions in hemorrhagic and thromboembolic events [121, 122]. Similarly, reductions in

hospital readmission rates have been demonstrated among patients who received education regarding therapy with low-molecular-weight heparin and fondaparinux, relative to patients who did not receive anticoagulant education [123]. However, patient education in and of itself will not likely be sufficient to mitigate the public health burden of anticoagulant ADEs at the population-based level [124]. For example, one study found that current warfarin patient information sheets provided at the time of dispensing often exclude recommended essential or important knowledge items and are at reading levels that are far above what is recommended for presentation of health information to laypersons [125, 126]. In addition, the extent and quality of anticoagulation education delivered outside of anticoagulation clinic services are difficult to assess through existing data sources.

Another core tenet of care transition models is medication reconciliation [79], commonly defined as “the process of reviewing a patient’s complete medication regimen at the time of admission, transfer, and discharge, and comparing it with the regimen being considered for the new setting of care” [127]. Medication reconciliation as a care transition strategy is important to reduce potential medication discrepancies. Although studies that have evaluated medication reconciliation have demonstrated a positive impact on reductions in medication errors or potential ADEs, an impact on reductions in actual medication-related harms (e.g., as reflected by emergency department visits or hospital readmissions for ADEs) remains to be seen [128, 129, 130, 131]. It remains unclear whether this is because medication reconciliation historically has not targeted the highest-risk drugs or patients or because it is probably insufficient alone, without additional postdischarge monitoring and care coordination (e.g., clinic-based support or home visits) [79, 129, 130]. Future studies should explore the incorporation of anticoagulant-targeted interventions in care transition strategies that include bundled strategies comprising medication reconciliation (e.g., ensuring appropriate transition from warfarin to NOAC), and hand-offs (e.g., ensuring that information about goal INR, dose, anticoagulant and/or primary care provider are communicated) across the continuum of care [79].

Incentives and Oversight

From the perspective of HHS, incentive and oversight levers potentially can be applied to advance anticoagulant ADE prevention through several strategies (**Appendix D**). Some of the HHS levers include statutory-based programs such as those noted in CMS programs related to coverage of services (e.g., National Coverage Determinations [NCDs]), financial incentive programs (e.g., EHR Incentive Program), and survey and certification processes (e.g., compliance with Conditions of Participation). Other

financial incentive programs, such as the EHR Incentive Program, can potentially be leveraged to facilitate and promote integration of anticoagulation management best practice principles into the overall health IT infrastructure. With that goal in mind, during development of the ADE Action Plan, the FIW for Anticoagulant ADEs collaborated closely with the HHS Office of the National Coordinator for Health IT (ONC) to identify health care quality measures specific to anticoagulant safety that were potentially amenable to incorporation into the EHR-based quality measure strategies; these measures are currently under exploration by ONC for possible incorporation into Stage 3 EHR Meaningful Use (MU) requirements. CMS quality reporting programs (e.g., Hospital Inpatient Quality Reporting, Physician Quality Reporting System, and Long-Term Care Hospital Quality Reporting) and quality rating systems (e.g., Five-Star Quality Rating System for nursing homes) are also critical mechanisms for quality improvement in health care, most notably through their use of clinical quality measure data for payment, public reporting, or to assist patients in identifying quality of care within facilities. Other CMS-related levers may exist within additional programs, such as Quality Improvement Organizations (QIOs). Maintaining and supporting positive impacts brought about by QIOs in their work to reduce ADEs could serve as an additional strategy for advancing Federal efforts to promote anticoagulation safety. Several of these programs are described in more detail in Section 4: “Incentives & Oversight Opportunities.”

Regardless of the specific strategy chosen to advance Federal incentives and oversight policies targeting anticoagulant ADE prevention, it will be important to develop policies that extend across health care settings (i.e., traverse inpatient to outpatient settings); reflect joint responsibility of the various provider groups (e.g., physicians, nurses, and pharmacists); can be shared across facilities/boundaries (e.g., through learning networks); can be closely evaluated for unintended consequences, including additional costs and burden to the health care system; can be continuously re-evaluated for relevance and impact; and can reflect alignment and consistency across the various Federal Agencies.

Federal partners should consider existing quality measures and initiatives to incentivize and advance anticoagulant ADE prevention efforts.

The ADE Action Plan recognizes that health care quality measures and quality reporting programs are an integral part of the HHS strategy for quality improvement in health care. Several Federal Agencies (e.g., AHRQ, CMS, VA) have well-established quality initiatives that provide important mechanisms for improving outcomes and protecting patient safety. Further exploration of these initiatives is warranted to evaluate the benefits, feasibility, and costs of incorporating new, validated measures of anticoagulant ADEs into these initiatives. These new measures can potentially complement efforts already underway to gauge and improve use of anticoagulants. For example, the CMS Hospital Compare program, which captures

information about quality of care from more than 4,000 Medicare-certified hospitals [132, 133], has newly incorporated important indicators of anticoagulation safety as part of publicly reported hospital quality measures (e.g., “Patients with blood clots who were treated with an intravenous blood thinner, and then were checked to determine if the blood thinner was putting the patient at an increased risk of bleeding” and “Patients with blood clots who were discharged on a blood thinner medicine and received written instructions about that medicine”) [132, 133]. Other federally endorsed patient safety and quality measures, such as AHRQ’s Patient Safety Indicators (PSIs) and Prevention Quality Indicators (PQIs), can potentially be explored for appropriateness and utility of incorporating complications of anticoagulation therapy [134]. PSIs provide information on potential in-hospital complications and adverse events following surgeries, procedures, and childbirth; PQIs are a set of measures that can be used with hospital inpatient discharge data to identify quality of care for “ambulatory care sensitive conditions” [134].

Current National Quality Forum (NQF)–endorsed measures of anticoagulation quality care mainly gauge appropriateness of anticoagulation use [135]. These measures are critical for assessing whether patients who are candidates for anticoagulation receive this therapy to meet the important goal of achieving reductions in stroke and other thromboembolic outcomes (e.g., VTE, PE), especially in light of data indicating underutilization of anticoagulation in patients for whom it is indicated [61, 62, 136]. However, there remains a need for measure concepts that track centrally important markers of anticoagulant safety (e.g., bleeding). The few currently available NQF-endorsed measures that address anticoagulant safety are mainly focused on surrogate markers of safe warfarin use (e.g., NQF #0555, NQF #0556). It may be necessary to explore new measure that: (1) reflect more updated approaches to optimizing anticoagulation management (e.g., percentage of patients with warfarin time in therapeutic range), (2) include metrics for safe use of agents other than warfarin (i.e., NOACs), (3) address patient populations who are especially vulnerable to ADEs (e.g., elderly) or are based in high-risk settings where such measure concepts do not currently exist (e.g., LTCs, nursing homes, home), and (4) assess clinical outcomes rather than surrogate indicators of anticoagulation safety (e.g., admissions or readmissions for anticoagulant-related bleeding rather than the number of times a laboratory value is obtained). This last component is important in that Federal quality initiatives have already moved toward development of measure concepts focused on clinical outcomes. Outcome-based measures will also be especially important for assessing safe use of NOACs, for which laboratory metrics of effectiveness and safety either are currently not available or are very limited [22]. It is important to recognize, however, that developing reliable outcome-based measures of anticoagulant safety can be challenging and will need to

be approached after adequate exploration of available data sources, since inadequate data sources or data quality can affect measure validity and feasibility. These challenges are caused in part by complexities inherent in collecting or accessing administrative claims, and chart-extracted or EHR data sources to reliably identify anticoagulant ADEs.

Regardless of which measures are chosen, any new metrics related to anticoagulant ADE prevention will need to reflect updated standards of care, be thoroughly tested and validated, be feasible and useful for reporting, and achieve adequate balance between newer and older anticoagulant agents, as well as between effectiveness (e.g., stroke) and safety (e.g., bleeding) outcomes. Both Federal partners and the non-Federal sector will also have an important role to play in facilitating ease and efficiency of reporting of any new anticoagulation ADE prevention measures by health care systems and providers. Moving forward, it will also be important for Federal partners to initiate discussions and collaborate with non-Federal organizations that also play a role in setting nationally recognized patient safety goals, standards, and quality measures (e.g., The Joint Commission, National Committee for Quality Assurance, Pharmacy Quality Alliance, and Institute for Safe Medication Practices). Such collaborations could facilitate further alignment and advancement of anticoagulation safety goals across Federal and non-Federal programs.

Opportunities to advance the prevention of anticoagulant ADEs through incentives and oversight-based strategies are summarized in **Figure 11**.

Figure 11. Federal Interagency Workgroup Recommendations for Actions That Can Potentially Advance Health Care Policy Strategies for Anticoagulant ADE Prevention

Actions That Can Potentially Advance Health Care Policy Strategies for Preventing Anticoagulant ADEs

- **Inpatient Settings**
 - Expand national health care quality reporting measures to include concepts related to multidisciplinary, systematic, and coordinated models of care (e.g., “Anticoagulation Stewardship”).
- **Outpatient Settings**
 - Expand national health care quality reporting measure sets to include measures specific to anticoagulant safety/anticoagulant ADE prevention.
 - Address payment/coverage barriers to uptake of evidence-based, high-quality ADE prevention strategies (e.g., anticoagulation clinics, warfarin PST/PSM).
- **Long-Term Care/Home Care**
 - Nursing homes: Address barriers to more integrated anticoagulation management (e.g., leveraging consultant pharmacist services to deliver anticoagulation management).
 - Home care: Address challenges in POC monitoring and barriers to more seamless communication of anticoagulation laboratory-testing results to anticoagulation management providers.

Abbreviations: ADE = adverse drug event; POC = point of care; PSM = patient self-management; PST = patient self-testing

Currently, there are few existing National Quality Forum–endorsed measures specific to anticoagulation safety.

To date, very few measures that are specific to anticoagulation safety have been endorsed by the National Quality Forum (NQF) (**Table 5**) [135]. Achievement of NQF endorsement is important, as certain CMS statutorily based programs require endorsement of proposed measures prior to adoption as clinical quality measures for Medicare beneficiaries. Furthermore, stakeholders such as hospitals and health insurance providers often adopt NQF-endorsed measures to improve quality of care for their patients and beneficiaries.

Table 5. National Quality Forum (NQF)-Endorsed Health Care Quality Measures Specific to Anticoagulation Safety*

Measure ID	Measure	Measure Description	Steward
NQF 0374	VTE Patients Receiving UFH with Dosages/Platelet Count Monitoring by Protocol (or Nomogram)	Number of patients diagnosed with confirmed VTE who received intravenous UFH therapy with dosages and platelet counts monitored using defined parameters such as a nomogram or protocol	The Joint Commission
NQF 0375	VTE Discharge Instructions	Number of patients diagnosed with confirmed VTE that are discharged to home, to home with home health or home hospice on warfarin with written discharge instructions that address all four criteria: compliance issues, dietary advice, followup monitoring, and information about the potential for adverse drug reactions/interactions	The Joint Commission
NQF 0555	Lack of Monthly INR Monitoring for Individuals on Warfarin	Average percentage of monthly intervals in which individuals with claims for warfarin do not receive an INR test during the measurement period	CMS
NQF 0556	INR for Individuals Taking Warfarin and Interacting Anti-Infective Medications	Percentage of episodes with an INR test performed 3 to 7 days after a newly started interacting anti-infective medication for Part D individuals receiving warfarin	CMS
NQF 0586	Warfarin PT/INR Test	Percentage of patients taking warfarin during the measurement year who had at least one PT/INR test within 30 days after the first warfarin prescription in the measurement year	Resolution Health, Inc.
NQF 0612	The percentage of patients taking warfarin who had PT/INR monitoring	Percentage of patients taking warfarin who had PT/INR monitoring	Active Health Management

*Note: Measures summarized in this table are specific to ensuring the safe use of anticoagulants (e.g., through patient education or laboratory monitoring). Measures related to ensuring that anticoagulants are prescribed for certain indications (e.g., receipt of VTE prophylaxis, anticoagulation therapy for AF at discharge) are not shown here.

Abbreviations: INR = international normalized ratio; PT = prothrombin time; UFH = unfractionated heparin; VTE = venous thromboembolism

Federal partners should address economic barriers to uptake of evidence-based anticoagulation ADE prevention strategies.

Improved and consistent utilization of evidence-based anticoagulation strategies (e.g., anticoagulation clinics, warfarin PST/PSM) will require considerations related to restructuring payment or coverage. Current economic barriers can be considered as falling into three broad categories: (1) limits on direct payment to nonphysician providers (i.e., pharmacists), who are the primary providers currently delivering care in anticoagulation clinics; (2) limits on physician billing for anticoagulation management services; and (3) challenges in the reimbursement structure for PST/PSM-based strategies.

Limits on direct payment to nonphysician providers (i.e., pharmacists) pose a serious challenge to wider provision of anticoagulation clinic services. Currently under Medicare Part B, pharmacists are considered “non-advanced practice staff” whose services are charged on the physician’s bill for provision of “supporting services” in physicians’ offices. Pharmacists, in collaboration with physicians, can only report medically necessary evaluation and management (E/M) services associated with managing anticoagulation therapy using “incident-to” Current Procedural Terminology (CPT) code 99211, when appropriate [137, 138]. CPT code 99211 is defined as “an office or other outpatient visit service rendered for the evaluation and management of an established patient, whose nature of presenting problem is ‘minimal,’ where at least 5 minutes of time is spent performing/supervising such services, and which does not require the presence of a physician.” This code can be limiting in that, despite providing a comprehensive patient evaluation and obtaining the clinical specimen (phlebotomy or finger stick), there may be limitations on the use of the billing code in the absence of such factors as adjustment of drug dosage, new medical co-morbidities, or dietary change [137]. Overcoming barriers related to achieving health care provider status for pharmacists in order to facilitate improved integration of anticoagulation clinic services in the delivery of day-to-day patient care will be critical in strategies aimed at anticoagulant ADE prevention. Nevertheless, this specific barrier is beyond the scope of the ADE Action Plan and is better addressed by other key organizations, such as the American Pharmacists Association (APhA). The APhA has identified increasing the value recognition and compensation for pharmacists’ clinical services as one of its top strategic priorities [139]. Other groups are also actively working to advance the recognition of pharmacists as health care providers [140].

There are high overhead costs associated with maintaining anticoagulation clinic services; this also serves as a barrier to more widespread adoption of anticoagulation clinic services. Limits on physician billing for these services also may be a barrier to more widespread adoption. Overhead costs impede

individual or small groups of physician providers (who are not part of an integrated health care system and cannot realize the direct cost savings through reductions in emergency department visits or hospitalizations) from initiating and maintaining coordinated anticoagulation clinic services. Currently, providers are limited to seeking reimbursement for PT/INR tests performed, and anticoagulation management services, including those provided via telephone calls (e.g., to report results of INR tests, provide patient education, explain changes in medication dosages), are not directly reimbursable. In the future, it may be necessary to explore whether the currently existing provider payment structure for outpatient anticoagulation-related visits fully captures the minimum services that are medically necessary to ensure optimal anticoagulation management, including all the processes of care required to minimize or prevent anticoagulant ADEs.

Improving access to point-of-care (POC) device testing in patients for whom warfarin PST/PSM is appropriate will also be important in overcoming current barriers to utilization of these particular anticoagulation management strategies [109, 141]. Several areas are amenable to exploration. These include: reevaluation of the adequacy of reimbursement rates for POC testing; minimizing delays in providers' being able to initiate PST/PSM for patients; clearly identifying patient populations for whom PST/PSM are the preferred management modalities (e.g., frail elderly and those residing in LTC facilities who may have physical barriers to accessing anticoagulation clinic services), and removing penalties or restrictions to their ability to access such care; resolving discordance in Medicaid reimbursement rates relative to Medicare rates for PST/PSM; and exploring the role of reimbursement for telephone-based management of patients using PST [109].

Moving forward, it will be important to address the aforementioned economic barriers so as to facilitate advancement of evidence-based ADE prevention strategies for warfarin and NOACs.

Health Information Technology (Health IT)

Limitations in the current health information exchange infrastructure, including lack of interoperability, serve as barriers to anticoagulant ADE prevention efforts.

Electronic exchange of health information, such as laboratory results and care (e.g., discharge) summaries, has been identified as a critical component of delivering optimal patient care; however, several barriers remain in health information exchange infrastructure [142]. For anticoagulation management specifically, improving bidirectional communication among multiple health care providers caring for the same patient may have a very important role in improving care transitions for patients,

especially those most vulnerable to anticoagulant ADEs (e.g., patients undergoing transitions across health care settings) [79, 143]. Health information exchange, as it relates to interoperability between pharmacy and laboratory systems, also affects safe delivery of anticoagulation. In spite of the recognition that enhanced laboratory–pharmacy linkages are key to improving the safety of medications such as anticoagulants [144], challenges remains in the ability of diverse EHR products to exchange this information so as to allow for delivery of more coordinated, effective, and efficient care [145]. Moving forward, policies and standards that better facilitate health information exchange will also facilitate improvement in care delivery, as it pertains to high-risk medications such as anticoagulants.

Opportunities to leverage EHR Meaningful Use requirements to advance anticoagulant ADE prevention should be considered.

During development of the ADE Action Plan, the FIWs for ADEs recognized the importance of health care quality measures in helping to advance ADE prevention efforts. In order to leverage the valuable interagency collaborations brought about during development of the ADE Action Plan, the FIW for Anticoagulant ADEs discussed and identified various health care quality measure considerations specific to anticoagulant ADE prevention and monitoring that were potentially amenable for incorporation into the EHR-based quality measure strategies. The FIW recommended a set of measure considerations (**Table 6**) to the Quality Measures Workgroup of the Health Information Technology Policy Committee. That committee, convened by the ONC, makes recommendations for candidate measures for the Stage 3 EHR MU requirements of the Medicare and Medicaid EHR Incentive Program. This will support and advance anticoagulant ADE prevention and monitoring. In making its recommendations, the FIW for Anticoagulant ADEs chose to recommend metrics based on clinical quality measures that were already in existence, had been endorsed nationally, and had previously undergone a critical review process, or metrics that closely mirrored processes or outcomes outlined by nationally recognized clinical guidelines. After initial recommendation, measures under consideration are submitted to CMS for further reviews, development, and testing. Final measure acceptance is dependent on rigorous and complete internal and external public reviews.

Table 6. Measure Considerations for EHR (Stage 3) Meaningful Use Requirements That Can Potentially Advance Anticoagulant ADE Prevention, as Proposed by the Federal Interagency Workgroup for ADEs

Metric	Description and Justification
Clinical Quality Measure Concepts—Eligible Providers (Outpatient Settings)	
1. Percent of patients on anticoagulants with INR test 7 to 14 days following out-of-range INR	<p>Proportion of patients</p> <ul style="list-style-type: none"> ▪ With nonvalvular AF ▪ On chronic warfarin therapy for >180 days before the start and during the measurement period ▪ With previously stable therapeutic INRs, who had an INR test 7 to 14 days after presenting with a single out-of-range INR below or above therapeutic during the measurement period
Rationale	<ul style="list-style-type: none"> ▪ Anticoagulation control, as measured by TTR, is improved by prompt, repeat testing after out-of-range INR values [146, 147] ▪ NQF Measure 0555 (see Table 5)
Clinical Decision Support (CDS) Rule Concepts—Eligible Providers (Outpatient Settings)	
2. INR Retesting Evaluation	Clinical notification to assess need for INR test in patients on chronic warfarin therapy (>180 days) and >30 days since last INR test*
Rationale	<ul style="list-style-type: none"> ▪ NQF Measure 0555 (see Table 5) ▪ 2012 ACCP (Chest) Guidelines—Recommendation 3.1: For patients taking VKA therapy with consistently stable INRs...[recommend] INR testing frequency of up to 12 weeks (Grade 2B). Stable INRs are defined as at least 3 months of consistent results with no need to adjust VKA dosing. When adjustments to the VKA dose are required, a cycle of more frequent INR monitoring should be completed until a consistent pattern of stable therapeutic INRs can be reestablished [4].
3. INR Testing—Interacting Anti-infective Medication	Clinical notification in patients on chronic warfarin therapy (>180 days) for whom treatment with interacting anti-infective medication is initiated to take one of the following actions: Instruct patients to hold warfarin dose, change anti-infective medication, notify anticoagulation provider, schedule INR retest.
Rationale	<ul style="list-style-type: none"> ▪ NQF Measure 0556 (see Table 5) ▪ 2012 ACCP (Chest) Guidelines—Recommendation 3.8: For patients taking VKAs avoid concomitant treatment with certain antibiotics (Grade 2C) [4]
Patient List Recommendation—Eligible Providers (Outpatient Settings)	
4. Last INR Test	<ul style="list-style-type: none"> ▪ Patient lists stratified by INR testing interval/time since last INR test (30 days, 60 days, 90 days, >90 days)
Rationale	<ul style="list-style-type: none"> ▪ NQF Measure 0555 (see Table 5) ▪ 2012 ACCP (Chest) Guidelines—Recommendation 3.1: For patients taking VKA therapy with consistently stable INRs...[recommend] INR testing frequency of up to 12 weeks (Grade 2B) [4]

Table 6. Measure Considerations for EHR (Stage 3) Meaningful Use Requirements That Can Potentially Advance Anticoagulant ADE Prevention, as Proposed by the Federal Interagency Workgroup for ADEs (continued)

Metric	Description and Justification
EHR Functionality/Usability Recommendation—Eligible Hospitals (Inpatient Settings)	
5. Inpatient Electronic Anticoagulation Management Flowsheet	<p>EHRs should have the capacity to display linked pharmacy and laboratory data pertinent to anticoagulation management. An inpatient electronic anticoagulation management flowsheet should display necessary data elements</p> <ul style="list-style-type: none"> ▪ In one location ▪ In an easily accessible format ▪ As near real-time as possible

Abbreviations: ACCP = American College of Chest Physicians; AF = atrial fibrillation; EHR= electronic health record; INR = international normalized ratio; NQF = National Quality Forum; TTR = time in therapeutic range; VKA = vitamin K antagonist (i.e., warfarin)

*Interval chosen to reflect that some patients may continue to be candidates for more frequent monitoring than every 12 weeks

Federal partners should continue to explore health care quality measures that target optimizing anticoagulation management.

The FIW for Anticoagulant ADEs considered additional metrics in its discussions and articulated areas where there are current gaps in national health care quality measures or EHR requirements as they pertain to anticoagulation safety (**Table 7**). Some of these measure concepts can be operationalized using non-EHR-based approaches; however, wherever feasible, development of these types of measures with the intent of future adoption by EHRs (including e-prescribing and clinical decision support tools) likely presents the most efficient and forward approach to measurement and minimizes reporting burden for health systems and providers. Health care quality metrics that can potentially be further developed and evaluated as discussed by the FIW included

- Dosing decision support tool for patients receiving chronic warfarin therapy who are not enrolled in a systematic and coordinated anticoagulation management program (e.g., anticoagulation clinic)
- Followup on individual time in therapeutic range (iTTR) <65 percent for patients receiving chronic warfarin therapy
- Identification of patients with increased risk for anticoagulant-related bleeding who require more frequent monitoring (e.g., HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly] score ≥ 3)

- Appropriate dosing (and if applicable in the future, laboratory outcomes) of NOACs
- Appropriate dosing of and laboratory outcomes for parenterally administered anticoagulant, in addition to low-molecular-weight heparin (e.g., UFH, argatroban)
- Metrics targeting clinical outcomes (e.g., bleeding events) versus limited to process measures
- Metrics targeting transitions of care-based measures (e.g., hospital followup with ambulatory care providers on discharge)

Table 7. Possible Areas for Health Care Quality Measure Concept Development Related to Anticoagulant ADE Prevention and Current Barriers to Development

Measure Concept	Current Barriers to Development
NOACs <ul style="list-style-type: none"> ▪ Dosing, adherence, and transitions among older and newer agents 	Evolving and early science Lack of well-established laboratory markers for safety/ effectiveness (e.g., laboratory monitoring parameters)
Parenterally administered anticoagulants (hospital uses of anticoagulants) <ul style="list-style-type: none"> ▪ Pertinent laboratory monitoring parameters 	Lack of consensus and/or uniformity across sites as to what constitutes optimal process measures (e.g., interfacility variations in target aPTTs)
Outcomes-based metrics <ul style="list-style-type: none"> ▪ Bleeding events 	Quality of diagnostic and procedural coding for capturing anticoagulant-related bleeding events poorly explored to date
Care transitions-related metrics	Associated with complex, difficult-to-measure process metrics (e.g., hand-offs, communication between inpatient and outpatient providers)

Abbreviations: ADE = adverse drug event; aPTT = activated partial thromboplastin time; NOAC = new oral anticoagulant

Research (Unanswered Questions)

As anticoagulation management practices evolve and new anticoagulant agents are introduced into clinical practice, there are research opportunities that can potentially advance the field of anticoagulation safety and for which Federal resources could be leveraged. These unanswered questions are summarized in **Figure 12**.

Unanswered questions remain regarding the most efficient ways of identifying patients at highest risk for anticoagulant-related bleeding.

One area of future research that Federal partners may be able to support relates to the need to identify the impact of and reduce bleed rates in patients with underlying pathological lesions who are especially predisposed to bleed. This research could entail better evaluating strategies that facilitate selection of

the appropriate anticoagulation treatment, given the patient's history, or more efficiently identifying and implementing early preemptive treatment (e.g., colonoscopic polypectomy for patients with colorectal polyps, proton pump inhibitor therapy for patients with peptic ulcers). This research would comport with evaluation of strategies aimed at better understanding factors that contribute to anticoagulant-related bleeding risk (e.g., drug–drug interactions, concomitant use of antiplatelet drugs, and genomic polymorphisms).

Further research and real-world experience with NOACs are needed.

Clinical trials take place in controlled conditions and often exclude patient populations at highest risk for ADEs (e.g., older adults, children, pregnant women, patients with hepatic and renal insufficiency). This is also largely true for clinical trials that have been carried out to date for NOACs; for this reason, the safety and efficacy of NOACs in real-world settings requires further exploration. It will be important for Federal partners to support research that furthers development of the evidence base in key areas of NOAC management and safety, including (1) monitoring and assessing patients for medication adherence, which is critical for ensuring optimal anticoagulation control with the NOACs, given their short half-lives; (2) patient-centered approaches to selection of NOACs that balance an individual patient's risk of thromboembolism with the risk of bleeding and take into account the differences among these agents in their efficacy and safety profiles; (3) development, use, and interpretation of potential laboratory markers for NOACs; and (4) development and dissemination of effective strategies for reversal of major or life-threatening bleeding associated with NOACs. Cost-effectiveness studies comparing NOACs to warfarin will also be important [148, 149]. Future economic analyses should take into account factors relating to the real-world application of these agents, including medication adherence; special populations; level of anticoagulation control for warfarin, as measured by TTR; and costs of anticoagulation services. For the first time in more than 5 decades, health care providers are now faced with a multitude of medication choices for oral anticoagulation. Additional research is needed to assist providers in identifying appropriate candidates to initiate or transition to these new agents, taking into account a variety of patient-related factors, including indication for anticoagulation therapy, INR stability, geographical access to laboratory INR monitoring, history of medication nonadherence, co-morbid conditions, and concomitant drugs [22].

Advancing anticoagulant ADE prevention efforts will require that Federal partners address emerging issues associated with safe use of NOACs.

Although the introduction of NOACs represents a significant advancement in the management of thromboembolic disease, there are a number of challenges in use of NOACs, including: a lack of well-

established reversal strategies in the event of toxicity; the unclear role of clinical laboratory assays to monitor levels of effectiveness or safety (e.g., in the event of thromboembolic or hemorrhagic events, prior to invasive procedures, in the presence of interacting drugs or declining renal function); as well as lack of health care provider familiarity with their use [22]. In addition, much remains to be learned about NOACs in relation to their use in real-world scenarios (e.g., dosing in organ dysfunction, impact of drug–drug interactions). There appear to be two primary areas in which Federal partners could engage private sector stakeholders to facilitate ADE prevention strategies in relation to NOACs. First, Federal/private collaboration may be important for developing algorithms to facilitate selection of the optimal NOAC according to individualized, patient-centered, risk–benefit assessments (e.g., history of previous exposure to anticoagulants, history of INR stability, co-morbidities, concomitant medications, pharmacogenomics, costs, or clinical laboratory test results). Collaboration also could facilitate the development of consensus guidelines/tools that define the care processes that constitute high quality of care or adequate “monitoring” of NOACs. Second, Federal partners may be able to leverage the resources of organizations, such as the North American Specialized Coagulation Laboratory Association (NASCOLA) [150], to develop and disseminate clinical guidance for providers regarding appropriate use of laboratory monitoring parameters to monitor NOAC effectiveness and safety. Other research opportunities in the area of advancing NOAC safety include

- Management of severe bleeding episodes (e.g., reversal protocols)
- Peri-procedural management medication interruptions for surgical or invasive procedures
- Transitions among older and newer agents.

With regard to pharmacogenomic testing, there may be value in identifying patients who are at highest risk for anticoagulant-related harms from the various NOACs [117]. Identifying these patients would be especially important, given the lack of routine bedside clinical and laboratory monitoring capacity that is currently available for these agents and the need to aid providers to the fullest extent possible in selecting the agents most appropriate for their patient(s).

Figure 12. Federal Interagency Workgroup Recommendations for Actions That Can Potentially Advance Research Strategies for Anticoagulant ADE Prevention

Actions That Can Potentially Advance Research Areas for Anticoagulation Safety

Clinical Science Domain

(AHRQ, CDC, FDA, public–private sector collaborations)

- Identify barriers to utilization of anticoagulation clinic services and warfarin PST/PSM utilization.
- Identify factors that facilitate broader uptake of evidence-based anticoagulant ADE prevention strategies.
- Identify factors that contribute to interclinic variability among anticoagulation clinic services (e.g., differences in patient risk profiles, targeting of excessively narrow INR target ranges).
- Support development of tools that facilitate optimal real-world management of bleeding events related to NOACs, including development of algorithms to facilitate selection of the optimal anticoagulant agent according to individualized, patient-centered risk-benefit assessments (e.g., history of previous exposure to anticoagulants, co-morbidities, concomitant medications, pharmacogenomics, costs, clinical laboratory test results).

Laboratory/Bench-top Science Domain

(CDC, NIH, public–private sector collaborations)

- Support development and improvement of laboratory assays for NOACs (including monitoring levels of anticoagulation, predicting effectiveness/risk).
- Identify any remaining or new areas where pharmacogenomics-guided anticoagulation management may be useful, including those pertinent to NOACs.

Education Domain

- Support development and evaluation of educational tools and programs related to high-quality anticoagulation management for patients, caregivers, and health care providers.

Abbreviations: ADE = adverse drug event; INR = international normalized ratio; NOAC = new oral anticoagulant; PSM = patient self-management; PST = patient self-testing

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SECTION

6

Diabetes Agents

Magnitude of the Problem

According to the CDC, diabetes mellitus affects 25.8 million people or 8.3 percent of the U.S. population [1]. In 2010, the national prevalence of diagnosed and undiagnosed diabetes mellitus among persons 20 years of age and older was estimated to be about 25.8 million persons, or 11 percent of all persons in this age range. For those 65 years of age or older, the prevalence of diagnosed and undiagnosed diabetes was estimated to be 10.9 million persons, or 27 percent of all persons in this age group. Among the 26 million individuals living with diabetes, it is estimated that 95 percent have type 2 diabetes. Patients with type 2 diabetes are at increased risk for serious long-term complications, such as cardiovascular disease and kidney disease [1]. Insulin and oral diabetes agents play an important role in controlling glycemic levels in patients with diabetes mellitus, thereby helping to prevent these complications. Among adults diagnosed with either type 1 or type 2 diabetes, 18 percent take insulin only, 13 percent take both insulin and oral medication, 50 percent take oral medication only, and 18 percent do not take either insulin or oral medication [1].

Recognizing that not all diabetes agents are associated with severe hypoglycemia (e.g., metformin monotherapy), this section of the ADE Action Plan will use the term “diabetes agents associated with serious hypoglycemia” to refer to insulin and secretagogue oral agents, predominantly sulfonylureas. Because of inconsistent definitions in the literature, the FIW for Diabetes Agents ADEs has chosen to use the term “serious hypoglycemia,” recognizing that this terminology does not represent Federal or agency perspectives. For the purpose of this Action Plan, “serious hypoglycemia” is defined as requiring third-party assistance (e.g., from a family member and/or medical personnel, or leading to an emergency department visit or hospital admissions) or blood glucose lower than 40 mg/dL, recognizing that there is a gradient of severity in these episodes (discussed further below).

The increasing burden of serious hypoglycemic events has been recognized as an important public health issue, potentially affecting millions of persons [2, 3, 4, 5, 6]. Historically, many but not all agencies

and organizations have emphasized “intensive” glycemic therapy (defined as attempting to achieve HbA1c values < 7 percent) as a goal for “most” persons with diabetes. However, an increase in rates of serious hypoglycemic events among patients in intensive control groups compared with those in generalized control groups has now been observed in several clinical trials, such as ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluations), ACCORD (Action To Control Cardiovascular Risk in Diabetes) and VADT (VA Diabetes Trial), which noted an increase in the rate of serious hypoglycemic events among patients in their intensive control groups compared with those assigned to the more generalized control group [7, 8, 9, 10, 11]. This occurred in the absence of significant health benefit. In a large health maintenance organization, the risk for hypoglycemia tended to be higher in patients with either near-normal or very poor glycemic control [12].

Diabetes agents, including insulin and secretagogues, are common causes of hypoglycemic events across inpatient and outpatient health care settings.

Inpatient Settings

In a nationally representative sample of Medicare beneficiaries hospitalized in 2008, hypoglycemia was identified as the third most common ADE [13]. Nearly all identified cases of hypoglycemia in this report were considered to be preventable. In other studies, clinically significant hypoglycemia (defined as <40 mg/dL) has been identified in 0.4 percent of non-ICU patient days, 1.9 percent of ICU patient days, and 2 percent to 5 percent of hospitalized patients with diabetes [14, 15, 16]. Hypoglycemia, defined as <50 mg/dL, was reported to account for 2.8 percent of patient days, 1.8 percent of hospitalized days, and 7.7 percent of admissions across three separate studies [17, 18, 19]. In addition, on the basis of 25,145 hospital visits in the 2004 Medicare Patient Safety Monitoring System (MPSMS) sample, an estimated 10.7 percent of patients exposed to insulin or oral diabetes agents experienced an ADE [20].

The Institute for Safe Medication Practice (ISMP) has identified insulin as an inpatient high-alert medication [21]. Data indicate that approximately one-quarter of all patient safety incidents involving insulin resulted in patient harm, and insulin may be implicated in 33 percent of medication error–related deaths [21, 22, 23, 24, 25, 26]. Insulin-related medication errors have been reported across all units of the hospital and can occur at multiple stages of the medication use process, with the majority of errors occurring at the time of prescribing and administration [21, 22, 23, 24, 25, 26].

Outpatient Settings

Diabetes agents (i.e., insulin and oral agents) are among the most common medication classes resulting in U.S. emergent hospitalizations for ADEs [27]. Between 2007 and 2009, among persons older than 65 years of age, insulin was implicated in an estimated 13.9 percent of emergent hospitalizations and oral agents were implicated in 10.7 percent of U.S. emergent hospitalizations annually [27]. From 1999 to 2010, preliminary data indicate that rates of hospital admissions for hypoglycemic events among Medicare beneficiaries increased by 22.3 percent while the rates of hospital admissions for hyperglycemia significantly decreased [27]. However, these data may underestimate the magnitude of the problem, as most hypoglycemic episodes are often treated outside of the emergency department or hospital setting [28]. In a survey of persons with diabetes from a large HMO, the self-reported rate of serious hypoglycemia (i.e., needing third-party assistance) in the year prior to the survey was 30 percent for insulin, 9 percent for secretagogues, and 6 percent for other non-hypoglycemic medications [29, 30]. In addition, studies have shown that higher frequencies of severe/serious hypoglycemic events were associated with lower socioeconomic status, duration of the disease, and depression [31, 32, 33].

Long-Term Care (LTC) Settings

CMS data indicate that approximately 33.4 percent of individuals receiving services in a certified nursing home have either type 1 or type 2 diabetes [34]. Recent data regarding the burden of hypoglycemic events among individuals residing in LTC facilities are not available. However, the primary risk factors for hypoglycemia (e.g., advanced age, recent hospitalization, and polypharmacy) are highly prevalent among nursing home residents [35, 36].

National surveillance data for hypoglycemia need to better distinguish between serious and minor hypoglycemic events.

The American Diabetes Association (ADA) defines serious hypoglycemia as a situation requiring help from a third party (e.g., by family member, paramedic, or emergency department personnel) [31]. The ADA has also defined documented symptomatic hypoglycemia as an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 70 mg/dL. In contrast, mild or minor episodes are classified as events that are self-treated [31]. In clinical care, hypoglycemic events in patients with diabetes may be defined as an abnormally low plasma glucose concentration that exposes the individual to potential or actual harm [32, 37]. However, these definitions have not been consistently utilized in published studies. Thus, the incidence of hypoglycemia reported in the literature is varied, and incidence in those at highest risk for these events is unknown [32, 37].

Surveillance

Federal partners should promote efforts to collect accurate and timely data to more effectively measure burden and trends of hypoglycemic events.

Currently, a limited number of Federal surveillance systems have the capacity to assess the national scope of hypoglycemic events associated with diabetes agents. Examples of these systems are summarized in **Table 8**. Despite availability of these systems, several challenges remain in identifying hypoglycemic events associated with diabetes agents. First, definitions for hypoglycemia are variable, making comparisons of results among surveillance systems and the literature difficult. Second, many existing Federal and private sector health systems do not have sufficiently integrated data systems that can provide the comprehensive information necessary to identify persons at risk for hypoglycemic events and enable precise categorization of numerators and denominators across the continuum of care. Third, existing surveillance metrics may need to be revisited to ensure accuracy, reliability, and clinical relevance consistent with current medical knowledge. Finally, the accuracy of diagnostic and procedural codes (International Classification of Disease [ICD] codes, including External Causes of Injury [E-codes]) for identifying hypoglycemic events need to be further evaluated; the limited data that are available, however, suggest an algorithmic approach to use of such codes is necessary to reliably capture hypoglycemic events associated with diabetes agents [38]. The development of more robust EHR systems can potentially support the creation of new clinical quality measures and decision support tools to facilitate improvements in the identification and management of patients with hypoglycemia.

Table 8. Summary of Metrics Related to Diabetes Agent ADEs (Hypoglycemia), Collected by Federal Surveillance Systems

Geographic Scope	Data Collection Methods	Diabetes Agent ADE or Management Metrics: Inpatient Setting	Diabetes Agent ADE or Management Metrics: Outpatient Setting
National ADE Incidence	Administrative claims and/or EHR data	AHRQ (HCUP):* <ul style="list-style-type: none"> Inpatient stays with ICD-9-CM (962.3) codes and E-codes (E932.3) 	FDA (Sentinel Initiative, Mini-Sentinel): ** <ul style="list-style-type: none"> ED visits, hospitalizations for hypoglycemic events
National ADE Incidence (+/-Rates)	Medical record review	AHRQ (MPSMS): *** <ul style="list-style-type: none"> Inpatient stays with combination of laboratory triggers (e.g., glucose ≤50 mg/dL or glucose ≤70 mg/dL but >50 mg/dL) and clinical triggers (e.g., administrations of D50) 	CDC (NEISS-CADES): <ul style="list-style-type: none"> ED visits, emergent hospitalizations for laboratory abnormalities, hypoglycemic events as diagnosed by clinicians, and documented in medical record narrative
National ADE Incidence	Administrative data and survey data	<ul style="list-style-type: none"> Not available 	AHRQ (NEDS): <ul style="list-style-type: none"> Derived from AHRQ’s State ED databases and from State inpatient database Used to estimate number of events (i.e., numerator data)

Table 8. Summary of Metrics Related to Diabetes Agent ADEs (Hypoglycemia) Collected by Federal Surveillance Systems (continued)

Geographic Scope	Data Collection Methods	Diabetes Agent ADE or Management Metrics: Inpatient Setting	Diabetes Agent ADE or Management Metrics: Outpatient Setting
			<ul style="list-style-type: none"> ▪ ED visits with hypoglycemia as first-listed diagnosis were identified using a validated algorithm. ▪ Estimates of population with diabetes from NHIS were used in the calculation of rates. <p>CDC (National Health Interview Survey, NHIS)</p> <ul style="list-style-type: none"> ▪ Estimates of civilian, non-institutionalized U.S. population with diabetes (denominator data that can be used for calculation of ADE rates)
National-, Regional-, Facility-level Spontaneous Reports	Voluntary reporting	<p>DOD (Patient Safety Reporting System)</p> <ul style="list-style-type: none"> ▪ Any clinician-diagnosed or patient-reported ADEs <p>FDA (FAERS):</p> <ul style="list-style-type: none"> ▪ Any clinician-diagnosed or patient-reported ADEs <p>VA (VA ADERS):</p> <ul style="list-style-type: none"> ▪ Any clinician-diagnosed or patient-reported ADEs 	<p>DOD (Patient Safety Reporting System)</p> <ul style="list-style-type: none"> ▪ Any clinician-diagnosed or patient-reported ADEs <p>FDA (FAERS):</p> <ul style="list-style-type: none"> ▪ Any clinician-diagnosed or patient-reported ADEs <p>VA (VA ADERS):</p> <ul style="list-style-type: none"> ▪ Any clinician-diagnosed or patient-reported ADEs
Regional-/ Facility-level ADE Incidence (+/- Rates)— Quality Improvement	Administrative claims and/or EHR data	<p>IHS (Resource and Patient Management System [RPMS-EHR])</p> <ul style="list-style-type: none"> ▪ Adverse Reaction Tracking (ART) System entry related to a diabetes agent ▪ EHR entry in the Problem List of “hypoglycemia” <p>VA (Integrated Databases):</p> <ul style="list-style-type: none"> ▪ ADE identified by ICD-9-CM codes, primary hospitalizations, emergency department or clinic visits, and laboratory values (blood glucose, HbA1c). An algorithm has been developed and validated to identify hypoglycemia in VA patients. 	<p>DOD (Pharmacovigilance Defense Application System):</p> <ul style="list-style-type: none"> ▪ Outpatient clinic visits, ED visits, hospitalizations using relevant ICD-9-CM codes and/or CPT codes <p>VA (Integrated Databases):</p> <ul style="list-style-type: none"> ▪ ADE identified by ICD-9-CM codes, primary hospitalizations, emergency department or clinic visits, and laboratory values (blood glucose, HbA1c). An algorithm has been developed and validated to identify hypoglycemia in VA patients. <p>IHS Resource and Patient Management System (RPMS-EHR)</p> <ul style="list-style-type: none"> ▪ ART System entry related to a diabetes agent ▪ EHR entry in the Problem List or purpose of visit of “hypoglycemia”

*ICD-9-CM 962.3 refers to “Poisoning by insulins and antidiabetes agents,” and E932.3 refers to “insulins and antidiabetic agents causing adverse effects in therapeutic use.”

**Currently, FDA Sentinel initiative covers more than 125 million lives; however, these do not constitute a nationally representative sample.

***In 2015, MSPMS will be replaced by the Quality and Safety Review System (QSRS).

Abbreviations: ADE = adverse drug event; ART = adverse reaction tracking; CPT = Current Procedural Terminology; D50 = 50 percent dextrose; ED = emergency department; EHR = electronic health record; HbA1c = hemoglobin A1c; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; mg/dL = milligrams per deciliter; NHIS = National Health Interview Survey

Federal partners should support use of standardized definitions of hypoglycemia and reporting of hypoglycemia in national surveys to advance surveillance efforts.

Actions that can potentially advance surveillance strategies for ADEs from diabetes agents are summarized in **Figure 13**. National surveillance using population-based sampling or administrative claims data may be efficient ways of collecting nationally representative data on serious hypoglycemic events. These studies can provide estimates of the national burden. For example, CDC's National Health Interview Survey (NHIS), a cross-sectional household survey of noninstitutionalized civilians in the United States, contains questions about diabetes status and treatment. NHIS may provide an opportunity for increased surveillance of hypoglycemic events on a population health basis. Questions related to the presence and frequency of hypoglycemic events could potentially be considered for incorporation into such national health surveys.

However, reducing ADEs requires individual providers and patients to act at the point of care. Federal Agencies that provide direct care to patients can go beyond retrospective approaches to implement proactive clinical approaches that utilize electronic health records (EHRs) and telehealth for identification and surveillance of patients who are at risk for hypoglycemia.

Figure 13. Actions That Can Potentially Advance Surveillance Strategies for Diabetes Agent ADEs

Actions That Can Potentially Advance Surveillance Strategies for Diabetes Agent ADEs

- **Address gaps in standard surveillance definitions for hypoglycemic events.**
 - Clearly define both severe/serious and mild hypoglycemic events.
 - When possible, confirm findings of surveillance data with medical record review to minimize opportunities for bias or misclassification.
- **Assess the adequacy of diagnostic and procedural coding for identifying hypoglycemic events.**
 - Assess specificity, sensitivity, PPV, and NPV of ICD and CPT codes for capturing hypoglycemic events.
- **Coordinate efforts across the Federal Government and the private sector to enhance inpatient monitoring of hypoglycemic events.**
 - Refine AHRQ Common Formats utilized by Patient Safety Organizations to include data on hypoglycemic events.
 - Identify whether existing national patient safety reporting systems (e.g., CDC’s National Healthcare Safety Network) could be used to facilitate inpatient tracking and monitoring of hypoglycemic events.
- **Improve availability and access to integrated EHR data with linked pharmacy, laboratory, and outcomes (e.g., admission–discharge) data at national and local levels.**
- **Improve efforts to collect additional information on hypoglycemic events within the ambulatory setting (e.g., events resulting in emergency department visits or hospitalizations).**
 - Consider utilizing surveys such as the Medicare Current Beneficiary Survey (MCBS), the National Health and Nutrition Survey (NHANES), and the National Health Interview Survey (NHIS) to collect population-based estimates of hypoglycemic events.

Abbreviations: ADE = adverse drug event; CPT = Current Procedural Terminology; EHR = electronic health record; ICD = International Classification of Diseases; MCBS = Medicare Current Beneficiary Survey; NHANES = National Health and Nutrition Survey; NHIS = National Health Interview Survey; NPV = negative predictive value; PPV = positive predictive value

Evidence-Based Prevention Tools

The American Diabetes Association (ADA) Standards of Medical Care in Diabetes and the ADA/American Geriatric Society (AGS) guidelines, as well as the Department of Veterans Affairs and Department of Defense (VA/DOD) guidelines, all interpret the scientific evidence as supporting individualization of

target glycemic goals based on life expectancy, co-morbid conditions, social support, and personal preference [39, 40, 41, 42]. The AGS, in the context of the American Board of Internal Medicine Foundation’s Choosing Wisely Campaign, has indicated that the use of medications other than metformin to lower HbA1c to <7.5 percent in most persons with type 2 diabetes aged 65 or older is not warranted [43]. This recommendation is based on the potential of harms (relative to that of benefit) noted when patients have major co-morbid conditions or limited life expectancy [43, 44]. **Figure 14** identifies currently existing Federal resources that address diabetes management and that can potentially be leveraged to advance hypoglycemia prevention.

Figure 14. Federal Assets Related to Management of Diabetes Agents, as Identified by the National Quality Strategy Priorities

<u>Resources for Safer Care—Health Care Provider Knowledge</u>	
<ul style="list-style-type: none"> ▪ AHRQ: <ul style="list-style-type: none"> – Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update—Provides a systematic review of all oral diabetes medications, including evidence about the risk of hypoglycemia ▪ BOP: <ul style="list-style-type: none"> – Management of Diabetes Clinical Practice Guidelines—Provides recommendations for the medical management of Federal inmates with diabetes ▪ DOD/VA: <ul style="list-style-type: none"> – Clinical Practice Guidelines for the Management of Diabetes—Provides structured framework to help improve patient outcomes, along with evidence-based guidelines and identification of outcome measures ▪ FDA: <ul style="list-style-type: none"> – Risk Evaluation and Mitigation Strategy—Mandatory risk management plans that use risk minimization strategies beyond professional labeling to ensure that benefits of medications outweigh their risks ▪ IHS: <ul style="list-style-type: none"> – Standards of Care and Clinical Practice Recommendations: Type 2 Diabetes—Provides guidance to clinicians and educators with regularly updated recommendations, useful clinical tools and resources, patient education material and a bibliography – Diabetes Treatment Algorithms—Developed to provide clinicians with a quick reference based on national guidelines, these algorithms reflect a collaborative effort between Indian health system professionals. Cards can be accessed by mobile devices and/or printed for use in the clinical setting. – Quick Guide Cards—Summarize important elements of care, including the importance of individualized target setting for HgA1c – Advancements in Diabetes Seminars—Hour-long live virtual seminars that provide CME/CE credit and feature updates on appropriate treatment for patients with diabetes including practical tools ▪ NIH: <ul style="list-style-type: none"> – National Diabetes Information Clearinghouse—Information on diabetes blood tests 	

Figure 14. Federal Assets Related to Management of Diabetes Agents, as Identified by the National Quality Strategy Priorities (continued)

<p style="text-align: center;"><u>Resources for Patients and Family Engagement</u></p> <ul style="list-style-type: none"> ▪ ACL: <ul style="list-style-type: none"> Community organizations offer various programs that have been or are currently supported in part by Federal funds, such as <ul style="list-style-type: none"> – Stanford Diabetes Self-Management Program—6-week program to help participants better manage their diabetes, including information about methods to deal with symptoms of hypoglycemia – National Council on Aging Better Choices, Better Health-Diabetes—6-week online workshop to learn self-management techniques, including curriculum on hypoglycemia – HomeMedsSM Medication Management System—Multidisciplinary collaborative providing patient counseling, reassessment, and adjustment of medication regimens for older adults in various nonacute health care settings (e.g., home care) ▪ AHRQ: <ul style="list-style-type: none"> – Medicines for Type 2 Diabetes: A Review of the Research for Adults—Summary of research on benefits and possible side effects of diabetes agents to guide patients in discussions with their health care provider – Premixed Insulin for Type 2 Diabetes: A Guide for Adults—Guide compares benefits, side effects, and costs of a newer type of premixed insulin with other kinds of insulin and pills for diabetes – Methods for Delivering Insulin and Monitoring Blood Sugar: A Review of the Research for Children, Teens, and Adults With Diabetes—Discusses what research says about different ways to measure blood sugar and take insulin ▪ FDA: <ul style="list-style-type: none"> – Medication Guides (available for a variety of diabetes agents, including sulfonylurea-thiazolidinedione combination product) ▪ NIH: <ul style="list-style-type: none"> – What I Need to Know About Diabetes Medicines—Online resource which includes guidance on hypoglycemia – Hypoglycemia—Resource defining hypoglycemia, potential causes, treatment, and prevention (available in National Diabetes Information Clearinghouse) – National Diabetes Information Clearinghouse—Information on diabetes blood tests ▪ NIH/CDC: <ul style="list-style-type: none"> – Know Your Blood Sugar Numbers—Resource on how to test blood glucose level (produced by National Diabetes Education Program)
<p style="text-align: center;"><u>Resources for Communication and Coordination of Care</u></p> <ul style="list-style-type: none"> ▪ AHRQ: <ul style="list-style-type: none"> – Project RED—Includes a number of medication-related strategies (e.g., active medication reconciliation, medication teaching for patients and caregivers, development of medication list for patients and their health care providers) ▪ NIH/CDC: <ul style="list-style-type: none"> – Helping the Child with Diabetes Succeed: A Guide for School Personnel—Resources for school personnel with guidance on preventing and treating hypoglycemia at school (produced by National Diabetes Education Program)

Inpatient settings

Appropriate glycemic control in inpatient settings requires a careful balance in managing the risks associated with both hyperglycemia and hypoglycemia. Target values for glycemic control recommended by the Federal sector and multiple private and public stakeholder agencies should be

individualized. Each patient would thus need an individual approach toward mitigating the risk of hypoglycemia. Uncontrolled hyperglycemia has been associated with poor outcomes in a dose/response relationship, and use of intensive insulin therapy has been associated with reductions in mortality in epidemiological studies and high visibility single-site randomized trials in ventilated ICU (mixed surgical and nonsurgical) patients [45]. However, these results were not replicated in a large, multicenter trial (the NICE-SUGAR study), in which serious hypoglycemia was increased in the intensive insulin therapy arm and associated with increased mortality [46]. Professional society-recommended upper-level glycemic targets in the ICU setting range from 150 mg/dL (Society of Critical Care Medicine) to 200 mg/dL (American College of Physicians). The strength of evidence for glycemic control in non-ICU settings is of low quality [47].

Federal partners should facilitate the use of systems that enhance recognition and documentation of risk factors that contribute to inpatient hypoglycemic events.

The risk for hypoglycemic events may be increased due to numerous hospital-, provider-, and patient-related risk factors and actual events can result from iatrogenic factors, especially related to administration of medications. There are a number of individual patient characteristics that may increase an individual's likelihood of experiencing a hypoglycemic event, including low body mass index (BMI), cachexia, age, and congestive heart failure. Iatrogenic factors include using insulin and/or oral hypoglycemic agents too aggressively, inappropriately, or without sufficient followup in the hospital setting. Hypoglycemic events also can result if there are additional changes in a patient's drug regimen that alter insulin resistance (e.g., treatment with corticosteroids) or the metabolism of hypoglycemic agents [48, 49, 50].

The use of insulin and oral diabetes agents, failure to adjust diabetes regimens in response to decreases in oral intake, and unexpected deviation from normal hospital routines have been identified as common risk factors in iatrogenic hypoglycemia [50]. Unexpected interruption of tube feedings or other sources of nutrition and failure to respond appropriately to an initial hypoglycemic event are also among the most common, and potentially most preventable, sources of iatrogenic hypoglycemic events. Studies have shown that more than 40 percent of patients who experience one iatrogenic episode go on to suffer at least one additional distinct hypoglycemic event that is largely preventable [50]. It is critical that clinical judgment, not metrics, guide medication administration and glycemic targets for individual patients.

Effective prevention of inpatient diabetes agent adverse events requires multidisciplinary coordination.

A systematic approach is essential to promoting the safe and appropriate use of insulin in inpatient settings. Medication errors can occur at multiple stages in the medication process. Therefore, information should be shared across all health care providers and shifts. This includes documentation of all nutritional intake, coordination of meal time/blood glucose testing, as well as any changes in normal routine (e.g., reduced dietary intake or use of parenteral nutrition). The use of an EHR, as well as the use of order sets and medication protocols, can support templates for tracking this information. Clear documentation of any initial event is important to support coordination across all inpatient health care providers, as is the sharing of template order sets such as those in use by the VA [51]. For ICU patients in the VA, this dashboard reports quarterly the proportion of patient days on a hypoglycemic agent with any hypoglycemic event (glucose ≤ 45 mg/dL and/or ≤ 60 mg/dL) and the proportion of patients on hypoglycemic agents with a mean glucose >180 mg/dL, as well as risk-adjusted outcomes [52, 53]. These efforts are supported by shared resources, including the VA/DOD guidelines, template order sets to manage hyperglycemia and hypoglycemic events, references, a special section on reducing hypoglycemic events, and other educational materials. Similarly, efforts to reduce inadvertent interchanges between medications that are commonly mistaken for one another (e.g., U-500 and U-100 insulin) can enhance prevention efforts by ensuring that medications that may look alike or sound alike are clearly labeled and stored separately [21, 22, 23, 24, 25, 26, 45, 46, 48, 49, 50, 54, 55].

Efforts are underway to evaluate effectiveness of implementing specific strategies to reduce the prevalence of hypoglycemic events in inpatient settings.

One CMS-funded effort, the Partnership for Patients (PfP) Initiative, is currently testing the scaling of prevention strategies for hypoglycemic event prevention in inpatient settings. A multiphase approach with the following elements was used with the aim of decreasing hypoglycemic events:

- Adopting a basal/bolus insulin protocol
- Instituting a nurse-driven protocol for hypoglycemia
- Ensuring the coordination of mealtime blood glucose testing, insulin administration, and meals

Other opportunities for advancing diabetes agent ADE prevention strategies/tools in inpatient settings are summarized in **Figure 15**.

Figure 15. Opportunities for Advancing Diabetes Agent ADE Prevention Strategies/Tools, as Identified by the National Quality Strategy Priorities—Inpatient Settings

<p style="text-align: center;">Patient and Family Engagement</p>	<ul style="list-style-type: none"> ▪ Individualized target setting <ul style="list-style-type: none"> – Acknowledgment of patient risk factors (e.g., BMI, cachexia, age, CHF, advanced malignancy, renal or liver disease) – Understand iatrogenic factors (e.g., nutritional intake, patient compliance, regimen change) ▪ Educate patients on any self-management implications of changes to insulin regimen using teach back method ▪ Educate patients on use of products for treating low blood glucose, including over-the-counter products [56] ▪ Provide hypoglycemia diabetes patient education materials ▪ Understand patient adherence with medication and diet regimen and daily barriers that patients encounter ▪ Consider the use of a standardized process to assess individual patient need for devices for self-administration in the event of an urgent or emergent hypoglycemic event [57]
<p style="text-align: center;">Effective Communication and Coordination of Care</p>	<ul style="list-style-type: none"> ▪ Multidisciplinary coordination and collaborative health care professional partnerships (including hospitalists, endocrinologists, nurses, pharmacists, and dietitians) throughout the medication process [58, 59, 60, 61, 62] ▪ Education of health care professionals on the importance of effective communication and coordination of care ▪ Engagement with pharmacists, nurses, dietitians, and other health care professionals at the time of discharge ▪ Minimize fragmentation of medical care ▪ Support development of tools that facilitate <ul style="list-style-type: none"> – Improved prescribing of diabetes agents to minimize the potential for medication errors – Improved identification of root causes of hypoglycemic events – Improved patient compliance to/adherence with medication/diet and daily barriers that patients encounter

Figure 15. Opportunities for Advancing Diabetes Agent ADE Prevention Strategies/Tools, as Identified by the National Quality Strategy Priorities—Inpatient Settings (continued)

<p style="text-align: center;">Science-Driven Prevention and Treatment</p>	<ul style="list-style-type: none"> ▪ Consider individual patient characteristics in selecting diabetes agents and glycemic targets ▪ Use protocols to <ul style="list-style-type: none"> – Assess risk during initial evaluation – Reassess risk periodically ▪ Assess cause of prior events ▪ Support development of standardized tools for insulin administration (e.g., insulin infusion protocols) ▪ Ensure consistency in order sets ▪ Use standardized, evidence-based order sets (avoid free text) ▪ Conduct root cause analysis of hypoglycemic events when appropriate ▪ Capture critical information associated with hypoglycemic events at admission or discharge: <ul style="list-style-type: none"> – Prior history of hypoglycemic episodes – Past diabetes medication management – Level of glycemic control – Assessment of patient’s cognitive abilities, literacy level, visual acuity, dexterity, cultural context, and financial resources for acquiring outpatient diabetic medications and supplies
<p style="text-align: center;">Promotion of Best Practices Within Communities</p>	<ul style="list-style-type: none"> ▪ Encourage multidisciplinary care coordination [31, 44] ▪ Consider individual patient circumstances (e.g., cognition, life expectancy, sedation) [31] ▪ Ensure professional supervision during any medication changes

Abbreviations: BMI = body mass index; CHF = congestive heart failure

Outpatient Settings

Because of the complexity of the patient population comprising those at highest risk of experiencing hypoglycemic events (e.g., older persons), the FIW reviewed several conceptual models to help guide the development of the strategic framework. Of the models reviewed, the most influential and comprehensive is the Chronic Care Model, which uses a systematic approach to restructuring medical care to create partnerships between health systems and communities [63, 64, 65]. To improve chronic care, the model includes system requirements for health care organizations, community resources, self-management support, delivery design, decision support, and clinical information.

Shared decisionmaking, which engages the patient, families, and other designated individuals in disease management, is an essential element of ongoing care. In order to participate in decisions related to the patient's illness in the context of his or her belief systems and culture, he or she must have sufficient information and must clearly understand it. Patients need to be both informed and engaged. As such, health care provider education should emphasize cultural competency, health literacy/numeracy, shared decisionmaking practices, and motivational interviewing [39, 63, 64, 66].

A key element of any strategy to reduce the risk of hypoglycemic events is recognizing the importance of existing co-morbid conditions that may affect adherence and risk of medication side effects, as well as physical function and quality of life. Type 1 diabetes and type 2 diabetes are chronic diseases. Management for the broad categories of diabetes will not be the same for everyone because of the differences in underlying etiology and the demographics of the affected populations, as well as the length of time from when the patient was diagnosed with diabetes. Co-morbid conditions are more common in patients with type 2 diabetes, particularly as they age [65, 67, 68, 69]. According to the Medical Expenditure Panel Survey (MEPS), most adults with diabetes have at least one co-morbid chronic disease and as many as 40 percent have at least three [69, 70, 71, 72]. Finally, throughout the aging process, individuals are at increased risk for co-morbid disease independent of diabetes [65, 67, 68, 69], which may complicate diabetes management and increase morbidity and mortality.

Self-management of hypoglycemia occurs almost exclusively in the ambulatory care setting. Management of hypoglycemic events in the home, school, workplace, and long-term care settings may reduce subsequent events that require emergency department visits or hospitalizations. Patient self-management may be affected by co-morbidities. Impaired renal function can prolong the half-life of insulin and alter sulfonylurea degradation, resulting in increased incidence of hypoglycemic events. Cognitive impairment adversely affects patients' ability to self-manage their diabetes and is associated with cardiovascular morbidity and mortality. Depression may also pose significant barriers to appropriate diabetes control by affecting the ability to maintain a healthy lifestyle, including exercise, good dietary habits, and adherence to a prescribed regimen [73, 74].

Federal partners should facilitate prevention efforts that are based on a patient-centered approach.

To date, outpatient prevention tools for hypoglycemic events have not explicitly recommended a comprehensive assessment of chronic co-morbid conditions as major contributing risk factors for hypoglycemia, in addition to social and educational factors. Use of a framework that identifies

contributing social determinants, as well as medical and mental health risk factors, can permit the development of individualized approaches to glycemic targets, medication side effects (including but not limited to hypoglycemia), and social and educational support.

Federal and private sector professional guidelines recommend educating patients, families, and caregivers regarding the parameters for diabetes medications, including timing with meals and activities, identifying blood glucose levels that require immediate provider notification, as well as blood glucose-level patterns that require notification on a more routine basis [31, 39, 40, 66]. National and international organizations such as The Joint Commission and the World Health Organization have developed guidelines to prevent ADEs associated with the use of look-alike, sound-alike medications [70, 71, 72]. Look-alike, sound-alike medications were identified as a National Patient Safety Goal (NPSG) by The Joint Commission and the Institute for Safe Medication Practices (ISMP) in 2005. For example, the NPSG identified that HumaLOG has been confused with HumaLIN. Organizations such as the ADA, The Joint Commission, and the ISMP have identified a number of recommendations for the care of older adults with diabetes to prevent hypoglycemic events [31, 44]. The National Diabetes Educational Program, jointly led by the National Institutes of Health and the Centers for Disease Control and Prevention, has also developed resources specifically for children and teens with diabetes [75, 76].

The most recent private sector and Federal guidelines recommend individualized targets based on life expectancy and the presence of chronic co-morbid conditions.

Federal partners should support strategies that incorporate shared decisionmaking in diabetes agent medication management, where appropriate.

In clinical settings in which there is no single or ideal diagnostic treatment regimen, shared decisionmaking is an important tool in guiding prescribing decisions. Several medical associations endorse shared decisionmaking [39, 40]. For example, the VA/DOD Clinical Practice Guidelines for the Management of Diabetes Mellitus in Primary Care (2010) as well as the American Diabetes Association and European Association for the Study of Diabetes (EASD) June 2012 joint position statement on hyperglycemia treatment all specifically note the importance of shared decisionmaking with the patient when choosing goals of therapy [39, 42]. Promoting shared decisionmaking is one of several opportunities for advancing diabetes agent ADE prevention strategies/tools in outpatient settings; these are summarized in **Figure 16**.

Figure 16. Opportunities for Advancing Diabetes Agent ADE Prevention Strategies/Tools as Identified by the National Quality Strategy Priorities—Outpatient Settings

<p style="text-align: center;">Safer Care</p>	<ul style="list-style-type: none"> ▪ Medication adjustments in response to changes in oral intake ▪ Coordination of meal time and blood glucose testing ▪ Care coordination across all health care professionals ▪ Medication reconciliation of diabetes medications ▪ Caution against use of sliding scale insulin in patients that may be at higher risk for hypoglycemia (e.g., older adults, those with dementia) ▪ Encourage a multidisciplinary care approach, including pharmacists, nurses, diabetes educators, dietitians ▪ Incorporate data from patient glucometers into the electronic health record to identify patients at risk
<p style="text-align: center;">Patient and Family Engagement</p>	<ul style="list-style-type: none"> ▪ Tools to establish individual patient goals ▪ Shared decisionmaking, including patient preferences ▪ Teach-back method in which patient is asked to explain the clinician’s instructions in his/her own words ▪ Train health care professionals on how to address cultural competency (literacy, language, cultural acceptability) ▪ Train health care professionals on how to address health literacy [58, 77, 78, 79, 80, 81, 82, 83] ▪ Awareness and education of patients/families on how to treat low blood glucose, including availability of products such as glucose tablets for home use [56] ▪ Understand patient compliance/adherence to medication and diet regimen and daily barriers patient encounters ▪ Explain risks of nocturnal hypoglycemia with patient and caregivers
<p style="text-align: center;">Effective Communication and Coordination of Care</p>	<ul style="list-style-type: none"> ▪ Provider training on effective use of decision aids ▪ Education of health care professionals on the importance of effective communication and coordination of care ▪ Health care professionals should be encouraged to ask their patients if they experience any challenges with diet and encourage dietitians to be part of this process ▪ Enhanced medication reconciliation at the time of hospital discharge [84]

	<ul style="list-style-type: none"> ▪ Patient education <ul style="list-style-type: none"> – Checking medication expiration date – Identification of home blood glucose goals – Detection and treatment of adverse events – Importance of consistent eating patterns – Guidance on sick day management – Information on accuracy of self-monitoring equipment
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Figure 16. Opportunities for Advancing Diabetes Agent ADE Prevention Strategies/Tools, as Identified by the National Quality Strategy Priorities—Outpatient Settings (continued)

<p>Science-Driven Prevention and Treatment</p>	<ul style="list-style-type: none"> ▪ Development and enhancement of decision aids [85] ▪ Provider coordination of any changes in medication ▪ Addressing inaccuracy of self-monitoring of blood glucose with patients and caregivers [86, 87, 88, 89]**
<p>Promotion of Best Practices Within Communities</p>	<ul style="list-style-type: none"> ▪ Multidisciplinary care coordination [39, 40, 41, 51] ▪ Consideration of individual patient circumstances (e.g., cognition, life expectancy, sedation) [39, 40, 41, 51] ▪ Professional supervision during any medication changes

* Section 3506 of the Affordable Care Act encourages greater use of shared decisionmaking in health care and funds an autonomous program that would develop standards for and certify patient decision aids.

** The acceptable accuracy of these devices permitted by FDA is ± 15 mg/dL of the results of the reference measurement at glucose concentrations < 75 mg/dL or ± 20 percent at glucose concentrations > 75 mg/dL [89]. International Standards Organization guideline permits ± 15 mg/dL for values < 75 mg/dl. Accuracy varies among meters [86, 87, 88], and additional error can be introduced by user parameters. These issues have recently been reviewed by the Food and Drug Administration [89].

Federal partners should advance efforts to identify the role care transitions play in contributing to hypoglycemic events.

Medication errors and ADEs have been linked to poor communication of instructions to the patient at the time of discharge [58, 59, 60, 61, 62]. This is particularly true for insulin regimens, which are inherently more complex to manage and administer than other types of chronic disease medications [90]. Because the day of discharge is not always conducive to retention of verbal instructions [58, 59, 60, 61, 62], clear written instructions can provide a reference for patients and their outpatient providers, and a format for medication reconciliation between inpatient and outpatient settings. In one study, an insulin-specific discharge instruction form provided greater clarity and more consistent directions for insulin dosing and self-testing of blood glucose (BG), in comparison with a generic hospital discharge form [58, 59, 60, 61, 62].

To assist with medication reconciliation during the transfer from inpatient to outpatient settings and to avoid postdischarge adverse events/complications that can result in readmission, AHRQ's *Medications At Transitions and Clinical Handoffs (MATCH)* toolkit for medication reconciliation is a tool that can potentially be used to help facilitate medication reconciliation during transitions of care [84].

The ADA recommends a team approach to transitions to outpatient care that includes physicians, nurses, pharmacists, medical assistants, dietitians, case managers, and social workers. ADA recommends that the transition to outpatient care begin with a hospital admission assessment that obtains

- Prior history of diabetes or hyperglycemia, its management, and the level of glycemic control
- Early assessment of a patient's cognitive abilities, literacy level, visual acuity, dexterity, cultural context, and financial resources for acquiring outpatient diabetic supplies, which allows sufficient time to prepare the patient for discharge [31, 44]

Other recommendations suggest that the following areas be reviewed and addressed before the patient is discharged from the hospital [40, 58, 59, 60, 61, 62]:

- Level of understanding related to his/her diagnosis of diabetes
- Self-monitoring of BG and explanation of home BG goals
- Definition, recognition, treatment, and prevention of hyperglycemia and hypoglycemia
- Identification of health care provider who will be responsible for diabetes care after discharge
- Information on consistent eating patterns
- Instructions on when and how to take BG-lowering medications, including administration of insulin
- Sick day management
- Proper use and disposal of needles and syringes

Incentives and Oversight

The Incentives and Oversight Opportunities section (Section 4) of the ADE Action Plan provides an overview of the existing Federal incentives and oversight resources that may be leveraged to help ADE

incidence overall. **Figure 17**, and the discussion that follows, outline incentives and oversight opportunities specific to the safe management of diabetes agents.

Figure 17. Federal Interagency Workgroup Recommendations for Actions That Can Potentially Advance Health Care Policy Strategies for Diabetes Agent ADE Prevention

Actions That Can Potentially Advance Health Care Policy Strategies for Preventing Diabetes Agent ADEs

- Update national health care quality reporting measures to better reflect more recent clinical guidelines regarding the need to individualize hypoglycemic risk targets.
- Expand nationally recognized health care quality reporting measures to include concepts related to multidisciplinary, systematic, and coordinated models of care for managing inpatient glycemic targets.
- Adopt health care quality reporting measures that reflect the latest advances in measurement science.
- Address payment/coverage barriers to uptake of evidence-based, high-quality ADE prevention strategies, such as use of patient engagement and health literacy principles.
- Expand Federal and industry health care quality reporting measures that reflect the need for individualization of glycemic targets that incorporate co-morbid conditions.
- Explore utility, feasibility, and validity of developing nationally recognized health care quality measures related to hypoglycemic events resulting in emergency department visits or hospitalizations from ambulatory care or community living settings.
- Improve EHR standards and tools to better identify patients at high risk for hypoglycemia.

Transitions of Care/Coordinated Care

- Address barriers to integrated communication and coordination across health care settings and providers.

Abbreviations: ADE= adverse drug event; EHR = electronic health record

The nationally endorsed quality measures that relate to the management of diabetes should be revisited to reflect changes in medical science and expanded to include measures of hypoglycemic events.

The National Quality Forum has endorsed a number of measures related to the management of diabetes. However, not all these measures reflect the latest evidence base related to hypoglycemia risks, and they have not yet been revisited to reflect the newest guidelines relevant to glycemic control from the ADA, VA/DOD, and AGS. Specifically, they do not exclude patients for whom HbA1c <8 percent would be inappropriate according to new guidelines, or stratify by medications (such as insulin). Neither do they address potential overtreatment in high-risk groups. Rates of hospital admissions for

hypoglycemia are not addressed as a preventable hospitalization. **Table 9** below outlines the measures related to diabetes care that are currently nationally recognized and in use by a number of Federal programs, including the Centers for Medicare & Medicaid Services' Physician Quality Reporting System.

Table 9. National Quality Forum (NQF)–Endorsed Health Care Quality Measures Specific to Diabetes Medication Management and Hospital Admissions*

Measure ID	Measure	Measure Description	Steward
NQF 0731	Comprehensive Diabetes Care**	This measure assesses the number of patients (18–75 years) who had each of the following: <ul style="list-style-type: none"> ▪ Hemoglobin A1c (HbA1c) testing ▪ HbA1c poor control (>9%) ▪ HbA1c control (< 8%) ▪ HbA1c control (<7%) for subset of patients <65 years of age with exclusions for certain co-morbid conditions ▪ Eye exam performed ▪ LDL-C screening ▪ LDL-C control (<100 mg/dL) ▪ Medical attention for nephropathy ▪ BP control (<140/90 mmHg) ▪ Smoking status & cessation advice 	NCQA
NQF 0272	Diabetes Short-Term Complications Admission Rate	The number of discharges for diabetes short-term complications per 100,000 population over the past year	AHRQ***
NQF 0060	Hemoglobin A1c (HbA1c) testing for pediatrics	The percentage of pediatric patients with diabetes who received an HbA1c test	NCQA
NQF 1789	Hospital-Wide All-Cause Unplanned Readmission Measure	The measure estimates the hospital-level, risk-standardized rate of unplanned, all-cause readmission after admission for any eligible condition (including diabetes) within 30 days of hospital discharge	CMS

*Note: Measures summarized in this table are specific to diabetes medication management and diabetes-related hospital admissions or readmissions. Measures related to ensuring proper disease state management of diabetes that are not associated with risk of hypoglycemia are not shown here.

** NQF 0731 assesses comprehensive diabetes care that includes elements not specific to monitoring the risk of hypoglycemia.

*** Does not include admissions for hypoglycemia.

Abbreviations: HbA1c= hemoglobin A1c

Health Information Technology (Health IT)

The FIWs for Diabetes Agent ADEs proposed EHR (Stage 3) Meaningful Use electronic clinical quality measures for EHRs, which can potentially advance diabetes agent ADE prevention.

The FIW for Diabetes Agent ADEs discussed and identified various health care quality measures specific to hypoglycemic agent safety that were amenable for incorporation into EHR-based quality measure strategies. One measure concept that is being considered is a measure based on administrative claims data (measure related to emergency department visits or hospitalizations due to hypoglycemia). The FIW recommended these measures (**Table 10**) to the Quality Measures Workgroup of the Health Information Technology Policy Committee, which is convened by the HHS Office of the National Coordinator (ONC) for consideration as possible candidate measures for Stage 3 EHR MU requirements [91]. After initial recommendation, measures under consideration are submitted to CMS for further reviews, development, and testing. Final measure acceptance is dependent on rigorous and complete internal and external public reviews.

Table 10. Measure Considerations for EHR (Stage 3) Meaningful Use Requirements That Can Potentially Advance Diabetes Agent ADE Prevention, as Proposed by the Federal Interagency Workgroup for ADEs

Metric	Description and Justification
Clinical Quality Measure Concepts—Eligible Providers (Outpatient Settings)	
1. Percentage of patients on sulfonylurea/insulin therapy with out-of-range HbA1c	Assesses patients aged 65 and older with HbA1c <7% on sulfonylurea or insulin therapy with one of the following chronic co-morbidities: <ul style="list-style-type: none"> ▪ Cognitive impairment/dementia ▪ Advanced microvascular complications ▪ Limited life expectancy ▪ Current substance use
Rationale	Providers should be alerted when patients are at high risk for hypoglycemia.
Clinical Decision Support (CDS) Rule Concepts—Eligible Providers (Outpatient Settings)	
2. Alert to potential risk for hypoglycemic events	Clinical reminder to identify patients at high risk for hypoglycemic event
Rationale	Provider should be notified when a patient is high risk and either take action or comment on why no action was taken.
3. Shared decisionmaking on HbA1c glycemic goals	Clinical guidance that glycemic target should be discussed and set through dialogue between patient and provider and mutually agreed-on target range incorporated into medical record
Rationale	HbA1c glycemic goal should be entered in a field that can record use of shared decisionmaking to identify target.

Metric	Description and Justification
4. Patient-Centered Action Plan	Clinical documentation of steps to be taken once patient is identified as high risk for hypoglycemic event
Rationale	Captures activities undertaken to acknowledge and reduce risk.
5. Flowsheet	Flowsheet with certain elements should be presented on a single page to the physician.
Rationale	Clinician can view appropriate considerations and recommended next steps for patients at high risk for hypoglycemia.
Patient List Recommendation—Eligible Providers (Outpatient Settings)	
6. Stratified patient list	Electronically generate patient list stratified by HbA1c and co-morbidities.
Rationale	Allow clinician to stratify individuals currently receiving hypoglycemic events agents therapy by their HbA1c value and certain co-morbidities that increase their risk for hypoglycemia.

Table 10. Measure Considerations for EHR (Stage 3) Meaningful Use Requirements that Can Potentially Advance Diabetes Agent ADE Prevention, as Proposed by the Federal Interagency Workgroup for ADEs (continued)

Metric	Description and Justification
Clinical Quality Measure Concepts—Eligible Hospitals (Inpatient Settings)	
7. Hypoglycemic events, serious	Total number of hypoglycemic events, divided by the number of patients administered a diabetes agent
Rationale	Calculates percent of hypoglycemic events for all inpatients receiving diabetes agents.
8. Hyperglycemia	Total number of hyperglycemic hospital days (defined as elevated glucose level), divided by all individuals with a diagnosis of diabetes mellitus who were administered antidiabetic agents (except metformin)
Rationale	<ul style="list-style-type: none"> ▪ Calculates percent of hyperglycemic events for all inpatients receiving diabetes agents. ▪ Serves as balancing measure to hypoglycemia measure.
9. Hypoglycemia, mild	Total number of days in which any hypoglycemic event (<70 mg/dL) reported, divided by total number of hospital days for patients receiving a diabetes agent
Rationale	Currently no system to effectively track and monitor episodes of hypoglycemia that do not result in need for third-party assistance.
10. Recurrent Hypoglycemia	Patients suffering at least one recurrent hypoglycemic event on a subsequent hospital day during the same hospital stay
Rationale	Patients suffering at least one recurrent hypoglycemic event on a subsequent hospital day during the same hospital stay.
EHR Functionality/Usability Recommendation—Eligible Hospitals (Inpatient Settings)	
11. Documentation of etiology of hypoglycemic event	Total number of hypoglycemic events, divided by all patients administered a diabetes agent

Rationale	Captures etiology and actions to take (checklist) to prevent future events
12. Alert to potential risk for hypoglycemic events	Clinical reminder and documentation of risk mitigation steps taken (checklist) when patient has experienced two or more blood glucose values of <70 mg/dL
Rationale	<ul style="list-style-type: none">▪ When there is a patient with repeated blood glucose values of <70 mg/dL, provider should be alerted for potential risk.▪ Provider should be provided list of options to prevent future episodes or document why no action taken.

Table 10. Measure Considerations for EHR (Stage 3) Meaningful Use Requirements that Can Potentially Advance Diabetes Agent ADE Prevention as Proposed by the Federal Interagency Workgroup for ADEs (continued)

Metric	Description and Justification
EHR Functionality/Usability Recommendation—Diabetes Agents Health Literacy/Numeracy (Inpatient & Outpatient Settings)	
13. Health literacy	Provision of patient education materials on diabetes medications that follow health literacy principles
Rationale	<ul style="list-style-type: none"> ▪ Patients need educational materials that are easy to comprehend when prescribed a diabetes agent. ▪ Materials should follow health literacy principles. ▪ Materials should be available in patients’ native language. ▪ Provider should ensure that the patient can understand and follow the materials.
14. Health numeracy	Test patient’s ability to calculate numeric values to ensure proper HbA1c levels.
Rationale	<ul style="list-style-type: none"> ▪ Critical to persons with diabetes self-management to avert potential harms ▪ Important when patient experiences changes in diet, exercise, or improper calculation of medication dose

Abbreviations: HbA1c = hemoglobin A1c; mg/dL = milligrams per deciliter

Research (Unanswered Questions)

As ADE prevention efforts evolve, key research opportunities have the potential to further advance the field of diabetes agent safety. These opportunities lie in areas such as health care provider education, patient education, surveillance, and incentives and oversight, and are summarized below, in **Figure 18**.

Figure 18. Federal Interagency Workgroup Recommendations for Actions That Can Potentially Advance Research Strategies for Diabetes Agent ADE Prevention

Actions That Can Potentially Advance Research Areas for Diabetes Agent Safety

Provider Education (AHRQ, CDC, FDA, public-private partnerships)

- Research on clinician decisionmaking and behavior related to prescribing and managing of diabetes agents (e.g., risk-benefit considerations, patient-centered prescribing, acceptance of principles of individualized care)
- Research on provider knowledge of HbA1c and point-of-care HbA1c testing, glucometer accuracy

Patient/Caregiver/Family Education (AHRQ, CDC, FDA, NIH, public-private partnerships)

- Research on the quality and impact of educational material for prevention of hypoglycemic events and other diabetes-related patient outcomes, and impact of individualizing glycemic targets
- Research on the quality and impact of health literacy and numeracy on the prevention of hypoglycemic events and other diabetes-related clinical outcomes
- Research the role of telephonic management of diabetes for certain patient populations for whom this modality may be appropriate

Surveillance and Prevention (AHRQ, CDC, FDA, public-private sector collaborations)

- Identify rates of serious hypoglycemic events in ambulatory care settings stratified by risk factors such as education level, health literacy, age, and co-morbid conditions.
- Identify how currently existing ADE prevention tools utilized during care transitions affect hypoglycemic events.
- Research the impact of co-morbid conditions (e.g., cognitive function) on hypoglycemic risks.
- Identify how EHRs and related tools (e.g., clinical decision support) could be leveraged to facilitate improved monitoring and prevention of hypoglycemic events.
- Improve integration of EHR data with pharmacy data to facilitate better identification of patients with diabetes and hypoglycemic events.
- Enhance data on rates of hypoglycemia and risk factors in long-term care settings.
- Evaluate how EHR-based medication management interventions affect patient outcomes.
- Evaluate impact of new methods of glucose monitoring (e.g., continuous glucose monitors).
- Further evaluate impact of hypoglycemic events on quality of life-related metrics.
- Identify potential opportunities for improvements in insulin packaging and evaluate impact of such improvements on the prevention of insulin medication-associated ADEs.

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SECTION

7

Opioids

Magnitude of the Problem

Prescription opioids are commonly used to treat acute and malignant pain, and, over the last decade, have increasingly been used in the management of chronic pain. Acute and chronic pain affect many Americans every year. Chronic pain alone is reported by more than 100 million Americans annually, with pain affecting more Americans than diabetes, heart disease, and cancer combined [1]. The annual costs of chronic pain, including medical costs of pain care and the economic costs related to disability days, lost wages, and lost productivity, range from \$560 billion to \$635 billion (in 2010 dollars) [1]. Although opioids are an essential tool for the treatment and management of acute, postoperative, and procedural pain, as well as for chronic pain related to cancer in the palliative care setting [1], use of opioids for chronic pain is more controversial because of the limited evidence surrounding the safety and efficacy of long-term opioid use for chronic pain [2]. Nevertheless, clinical practice guidelines recommend judicious use of opioids in appropriately selected and monitored patients [3].

The use of opioids has increased dramatically over the last decade. Between 1999 and 2010, the number of prescription opioids dispensed roughly doubled and the sales rate of prescription opioids (in kg/10,000 population) increased fourfold [4], with an estimated 201.5 million opioid prescriptions dispensed in 2009 [5]. In 2009, the prescription opioid hydrocodone was the single most commonly prescribed medication in the United States, and opioid analgesics were the third most commonly prescribed class of medications overall, leading the United States to spend approximately \$8.4 billion on opioids in 2010 [6]. This increased use of opioids has come with unintended and serious health and social consequences. There is limited evidence on the effectiveness of long-term use of opioids and it is not clear that the dramatic increase in the use of opioids has led to improved treatment of pain overall, especially of chronic pain [7].

Opioids cause a number of ADEs that affect patients in both inpatient and outpatient settings. These ADEs are detrimental to the health and quality of life of patients [8]. Opioid ADEs include oversedation and respiratory depression; gastrointestinal adverse events, such as nausea, vomiting, and constipation; opioid-induced hyperalgesia; pruritus; and immunological and hormonal dysfunction [9]. All these ADEs were considered by the Federal Interagency Workgroup (FIW) for Opioid ADEs as important possible targets of the ADE Action Plan; however, the FIW determined that addressing ADEs related to unintentional opioid overdoses (i.e., oversedation, respiratory depression) were the highest priority because of the associated mortality and morbidity. Opioid overdoses constitute a tremendous public health burden that is potentially amenable to measurable prevention efforts, and a coordinated action plan could aid in prevention.

Prescription opioid–related deaths are considered to be one of the Nation’s leading preventable public health problems.

Opioid overdose is a significant cause of drug-related injury and an important cause of adverse drug events. Opioids are central to the ADE Action Plan because they are a common cause of ADEs [10] and the leading cause of pharmaceutical overdose deaths [11]. By 2010, the number of prescription opioid overdose deaths had increased for the 11th straight year to 16,651 deaths [10], which exceeds the number of overdose deaths involving heroin and cocaine combined [10], and represents a quadrupling of the approximately 4,000 prescription opioid-related deaths reported in 1999 [10]. Moreover, the number of emergency department (ED) visits related to opioid misuse and abuse more than doubled from 2004 to more than 420,000 emergency department visits in 2011 [12]. Prescription opioid abuse is estimated to result in more than \$72 billion in health care-related costs each year [13].

Access to safe and effective pain care remains an important problem in the United States; efforts to minimize the burden of harms from opioids should be implemented in parallel with efforts to ensure patients suffering from pain receive the most effective and safest treatment available.

The Institute of Medicine report *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research* outlines the challenges faced by Americans affected by pain [1]. The Opioids Section of the ADE Action Plan is informed, in part, by the findings and recommendations of this seminal report. All recommendations in the ADE Action Plan should be taken in the context of improving overall patient care through providing the safest and most effective, evidence-based pain care. In pain care, treatment decisions require that the potential benefits of opioid analgesia be

weighed against the potential safety risks of opioid treatment. Therefore, these recommendations recognize the importance of the clinician’s judgment in the context of patient-centered care.

Because the dramatic increase in the use of opioids over the past decades is largely attributed to use for chronic pain, this section’s recommendations for safer outpatient opioid treatment will focus on long-term opioids used for chronic pain. However, safe opioid prescribing is needed in all settings, including acute, postoperative, and periprocedural situations.

Distinguishing overdoses that occur during the normal course of care from misuse/abuse will be important in efforts to prevent opioid ADEs.

The ADE Action Plan’s Opioids Section targets preventing opioid ADEs in patients prescribed opioids for pain, including patients who are injured through aberrant drug behavior. Discussion of patients who are prescribed opioids for addiction treatment, patients diverting opioids, and patients injured through suicide attempts is outside of the scope of the ADE Action Plan.

Although not specifically addressed in the ADE Action Plan, misuse and abuse of prescription opioids is an important public health problem and is the current target of several Federal and statewide initiatives by agencies such as the Centers for Disease Control and Prevention (CDC), Drug Enforcement Administration (DEA), Food and Drug Administration (FDA), National Institute on Drug Abuse (NIDA), Substance Abuse and Mental Health Services Administration (SAMHSA), and the White House Office of National Drug Control Policy (ONDCP). The FIW for Opioid ADEs acknowledges that there is a continuum of aberrant drug-related behaviors, and misuse and abuse are strong predictors for prescription opioid ADEs. The ADE Action Plan defers to the work of other Federal Agencies with regard to the specific issue of prescription opioid misuse and abuse.

The accurate categorization of opioid-related overdose deaths resulting from therapeutic use, versus misuse and abuse, is extremely challenging from a public health surveillance and epidemiologic perspective. Patients who are appropriately prescribed opioids can gradually drift into the spectrum of misuse/abuse through aberrant drug-related behaviors, such as increasing the dose or frequency of their opioids without consulting their prescriber [14]. This makes it difficult to target patients who are misusing/abusing opioids because it is challenging to identify patients who drift from therapeutic use to misuse/abuse. Aside from the practical difficulties in collecting data that can differentiate opioid ADEs from the normal course of care versus those arising from opioid misuse and abuse, the clinical definitions of addiction, dependence, misuse, and abuse are all still under debate within the pain

community [15]. The ambiguous definitions of misuse/abuse also make it difficult to draw conclusions from available data. As a result, the ADE Action Plan recommendations do not differentiate between patients who may misuse opioids. Instead, the Action Plan recommendations seek to reduce harm in all patients who are prescribed opioids for pain. The Action Plan supports developing a consensus on clinical and surveillance definitions of these terms but recognizes that this is outside of the scope of the plan. The ADE Action Plan does recognize the limitations of the data available and is cautious not to draw conclusions beyond those that the data can explain. For example, the CDC identified more than 16,651 opioid overdose deaths in 2010 [10], but it was not possible to distinguish deaths that occurred in the normal course of care when using medications as prescribed from deaths that resulted from intentional misuse and abuse. SAMHSA's Drug Abuse Warning Network (DAWN) estimated that more than 420,000 ED visits resulted from nonmedical use of prescription pain relievers in 2011 [12]. However, limited data are available about the number of ED visits for opioid ADEs during the normal course of care. Because of these limitations, much of the data cited throughout the opioid section of the ADE Action Plan may include patients who deliberately misuse/abuse opioids. These limitations are noted whenever applicable.

Surveillance

Understanding trends in opioid injuries and safe prescribing practices requires accurate, timely, and adequately representative information on key process and outcome measures—at national, regional, and facility levels.

A number of Federal- and State-based surveillance systems provide data on opioid ADEs. Broadly, these surveillance systems can be categorized as measuring three types of outcomes: (1) clinical (primary) outcomes (e.g., ED visits, deaths); (2) intermediate (surrogate) outcomes (e.g., clinical or laboratory values that precede or lead to clinical outcomes); and (3) process measures, indicators of actions aimed at mitigating the risk for clinical or intermediate outcomes (e.g., use of urine drug tests or State Prescription Drug Monitoring Program [PDMP] data). Clinical outcomes and process outcomes are most applicable to opioid ADEs because the prevention utility and role of intermediate outcomes is not clearly established. The identified Federal surveillance strategies have generally not been designed to assess intermediate outcomes related to opioid ADEs. A summary of Federal surveillance systems and selected State surveillance systems specific to opioid ADEs is presented in **Table 11**.

Currently available Federal surveillance systems outlined in the other sections are also capable of assessing the national opioid ADE burden. Federal systems involved in direct patient care (e.g., IHS, VHA) can capture regional- and facility-level information on the quality of opioid management. **Table 12** provides a summary of opioid ADE-related metrics from currently available Federal surveillance systems.

Table 11. Summary of Opioid ADE Metrics Collected by Federal and Relevant State Surveillance Systems

Source	Overview
National Vital Statistics System (NVSS), CDC	<ul style="list-style-type: none"> ▪ Collects data from all death certificates filed by States and territories in the United States, including deaths involving drugs. ▪ Uses ICD codes to identify the underlying causes of death (e.g., drug overdose) and contributing causes (e.g., specific pharmaceutical or illicit drugs).
Drug Abuse Warning Network (DAWN), SAMHSA	<ul style="list-style-type: none"> ▪ Collects data for drug-related ED visits from a nationally representative sample of U.S. non-Federal, short-stay, general medical and surgical hospitals with one or more EDs open 24 hours a day. ▪ Completed data collection in 2011; data are being incorporated into a larger National Center for Health Statistics (NCHS) survey.
Prescription Behavior Surveillance System (PBSS), CDC, FDA, BJA (under development)	<ul style="list-style-type: none"> ▪ Will collect de-identified data from multiple State Prescription Drug Monitoring Programs (PDMPs). ▪ Number of participating PDMPs continues to increase, with the goal of collecting nationally representative data to develop surveillance reports for each participating State.
Prescription Drug Monitoring Programs (PDMPs)	<ul style="list-style-type: none"> ▪ 49 States have legislative authority for PDMPs, and 47 States have active systems to collect State-level data related to the prescribing and dispensing of controlled substances. ▪ PDMPs collect patient, prescriber, dispensing pharmacy, and drug information.

Abbreviations: ADE = adverse drug event; BJA = Bureau of Justice Assistance; ED = emergency department; DAWN = Drug Abuse Warning Network; DEA = Drug Enforcement Administration; ICD = International Classification of Diseases; NCHS = National Center for Health Statistics; NVSS = National Vital Statistics System; PBSS = Prescription Behavior Surveillance System; PDMP = Prescription Drug Monitoring Program; SAMHSA = Substance Abuse and Mental Health Services Administration

Table 12. Summary of Metrics Related to Opioid ADEs Collected by Federal and Relevant State Surveillance Systems

Geographic Scope	Data Collection Method	Opioid ADEs or Management Metrics: Inpatient Settings	Opioid ADEs or Management Metrics: Outpatient Settings
National ADE Incidence/Rates	Administrative claims and/or EHR data	AHRQ (NIS): <ul style="list-style-type: none"> Inpatient stays with ICD-9-CM codes indicative of opioid ADEs 	AHRQ (NEDS): <ul style="list-style-type: none"> ED visits with ICD-9-CM codes indicative of opioid ADEs CMS (Medicare Part D Claims): <ul style="list-style-type: none"> Outpatient prescribing to detect fraud and abuse
	Medical-record review	AHRQ (MPSMS):* <ul style="list-style-type: none"> Opioids are not currently captured by MPSMS system, but will be included after the conversion to QSRS. 	CDC (NEISS-CADES): <ul style="list-style-type: none"> ED visits for opioid overdoses and other ADEs, not related to misuse/abuse CDC (NVSS-Mortality): <ul style="list-style-type: none"> Deaths due to opioid overdose SAMHSA (DAWN):** <ul style="list-style-type: none"> ED visits for opioid ADEs
Regional-/ Facility-level ADE Incidence/Rates (Quality Improvement)	Administrative claims and/or EHR data	<ul style="list-style-type: none"> Not available 	DOD: <ul style="list-style-type: none"> Outpatient clinic visits, ED visits, hospitalizations with ICD-9-CM codes and/or CPT codes VA: <ul style="list-style-type: none"> VA/DOD guideline-based process measures Outpatient clinic visits, ED visits, hospitalizations for opioid overdoses & other relevant ADEs per ICD codes and/or CPT codes and prescription data (e.g., naloxone Rx) VA/DOD/State PDMP: <ul style="list-style-type: none"> Number of opioids prescribed linked with patient and prescriber Number of patients with multiple opioid prescribers Number of patients on high daily dose of opioids
Spontaneous Reports		FDA: <ul style="list-style-type: none"> Clinician-diagnosed or patient-reported ADE 	FDA: <ul style="list-style-type: none"> Clinician-diagnosed or patient-reported ADE

Abbreviations: ADE = adverse drug event; ARCOS = Automation of Reports and Consolidation Order System; CPT = Current Procedural Terminology; DAWN = Drug Abuse Warning Network; DEA = Drug Enforcement Administration; ED = emergency department; EHR = electronic health record; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; PDMP = Prescription Drug Monitoring Program; QSRS = Quality and Safety Review System; SAMHSA = Substance Abuse and Mental Health Services Administration

* In 2015, MPSMS will be replaced by the Quality and Safety Review System (QRSRS).

** Surveillance using DAWN is currently undergoing transition to CDC's National Hospital Care Survey.

Outcome and process measures related to opioid ADEs are lacking.

Currently, few validated metrics are available to assess national- or facility-level burden of opioid ADEs. Opportunities for improvement include the development and validation of clinical outcome and process measures, standardized definitions for opioid ADEs, requirements for reporting, and research into validated metrics that can reliably identify opioid ADEs.

PDMPs and PBSS represent important opportunities for advancing surveillance to reduce opioid ADEs.

One of the opportunities for advancing surveillance is continuing to develop PDMPs and the PBSS so as to optimally capture the data needed to identify high-risk prescribing patterns and to better understand risk factors for opioid ADEs. Ideally, PDMPs should be able to track patients across settings (including across different States), identify high-risk prescribing practices, and alert prescribers to aberrant drug-related behaviors in patients prescribed opioids.

Future surveillance efforts should capture opioid ADEs on the basis of validated process and outcome measures, differentiate opioid ADEs that occur in the normal course of care from those arising from opioid misuse/abuse, and identify ADEs occurring during transitions of care.

A number of potential process measures—such as number and doses of opioids prescribed, number of patients with multiple prescribers, number of patients on high daily doses of opioids, and number of patients co-prescribed opioids and sedatives—are available through data collection sources, such as EHRs and PDMPs. Federal Agencies should explore the best methods to collect and manage these data to allow for accurate, real-time evaluation of trends in validated process measures. **Figure 19** summarizes the recommendations to advance surveillance strategies for opioid ADEs.

Figure 19. Federal Interagency Workgroup Recommendations for Actions That Can Potentially Advance Surveillance Strategies for Opioid ADEs

Actions That Can Potentially Advance Surveillance Strategies for Opioid ADEs

- **Determine the adequacy of diagnostic and procedural coding for capturing opioid-related overdose events.**
 - Assess specificity, sensitivity, PPV, and NPV of ICD and CPT codes for capturing opioid-related overdose events.
 - Develop, assess, and validate novel measures for identifying and recording opioid ADEs (outlined in **Table 15**).
- **Address strengths and limitations of using process measures to identify opioid ADEs.**
- **Study associations between process measures and risk of opioid ADEs in inpatient and outpatient settings.**
- **Improve access to more integrated EHR data with linked pharmacy and outcomes data.**
- **Identify appropriate ADE surveillance metrics for opioid ADEs in inpatient and outpatient settings.**
- **Develop better surveillance definitions for opioid-related overdose events.**
 - Clarify criteria for identifying opioid ADEs that occur in the normal course of care versus those arising as a result of opioid misuse and abuse.
- **Identify appropriate ADE surveillance metrics for opioid ADEs.**
- **Improve the capabilities and use of PDMPs.**
 - Promote increased use of PDMP systems by providers.
 - Maintain funding for PDMP development at the State and Federal level.
 - Strive for real-time data reporting and cross-setting interoperability for PDMPs.

Abbreviations: ADE = adverse drug event; CPT = Current Procedural Terminology; EHR = electronic health record; ICD = International Classification of Diseases; NPV = negative predictive value; PDMP = Prescription Drug Monitoring Program; PPV = positive predictive value

Evidence-Based Prevention Tools

Many evidence-based guidelines for prescribing opioids for chronic pain address the issue of opioid safety [3, 16, 17, 18, 19]. Specifically, the guidelines make patient-centered care central to the decisionmaking process through assessing patients at risk for opioid ADEs and balancing the goals of pain management with the risk of opioid ADEs. Risk factors for inpatient and outpatient opioid ADEs differ in a number of ways. In inpatient settings, system-wide changes may be the most important target for ADE prevention because many opioid ADEs occur from medication and prescribing errors and inadequate monitoring of patient outcomes. In outpatient settings, safer prescribing and monitoring by providers and patient-centered interventions are critical because problems such as inappropriate

medication use (e.g., inappropriate dose, issues of adherence, aberrant medication-related behavior) are likely to play a far larger role in causing opioid ADEs in these settings than in inpatient settings [14]. Federal Agencies have a number of strategies to promote safe opioid prescribing and reduce opioid ADEs; these can serve as a model for private stakeholders. Federal Agencies should continue to develop, study, and validate opioid ADE prevention strategies and promote the adoption of validated ADE prevention strategies throughout the continuum of care. Current and future Federal assets related to the safe management of opioid therapy are summarized in **Figure 20**.

Figure 20. Federal Assets Related to Safe Management of Opioid Therapy, as Identified by the National Quality Strategy Priorities

<u>Resources for Safer Care—Health Care Provider Knowledge</u>	
<ul style="list-style-type: none"> ▪ DOD/VA: <ul style="list-style-type: none"> – Opioid Prescribing Protocol/ Guidelines—Includes recommendations for assessing patients for appropriate pain therapy. – Education opportunities—Provider education Web portal (Talent Management System [TMS]) offers several continuing education courses on pain management, including a course on “Opioid Therapy for Acute and Chronic Pain.” – Opioid Safe Program at Womack Army Medical Center (Fort Bragg, North Carolina)—Primary care clinicians provide high-risk patients prescribed opioids with kits containing naloxone, along with training in identifying and responding to overdose symptoms. ▪ FDA: <ul style="list-style-type: none"> – Risk Evaluation and Mitigation Strategies (REMS)—Required strategy for extended-release and long-acting opioids; FDA developed a <i>Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics</i> and maintains a list of compliant continuing education (CE) programs for prescribers that include this curriculum. – Opioid Dose Conversion Table—Safe and reliable dose conversion table is based on updated evidence. ▪ IHS: <ul style="list-style-type: none"> – TeleBehavioral Health Center of Excellence Pain and Addictions course—15-series Webinar training program provides specialized training on how to treat pain and addictions. – “Pain Champion” Training—63-hour CE course trains local and regional experts, using the Project ECHO Model, which shares expertise by utilizing telehealth technology to connect an ECHO Team (primary care, specialists, and other providers integral to a patient-centered medical home team) to providers in rural and underserved locations. ▪ NIH: <ul style="list-style-type: none"> – NIDAMED Physician Education Tools—The National Institute on Drug Abuse (NIDA) created online tools and resources for medical professionals on safe pain management, including two classes entitled “Safe Prescribing for Pain” (2 CME/CE credits) and “Managing Pain Patients Who Abuse Rx Drugs”ⁱ (1.75 CME/CE credits). In addition to these two pain-focused educational resources, NIDA has developed an additional resource, “Substance Use Disorders in Adolescents: Screening and Engagement in Primary Care Settings,” which can be used by health care professionals to screen adolescents for aberrant prescription drug use and substance abuse disorders. ▪ SAMHSA: <ul style="list-style-type: none"> – Opioid Overdose Prevention Toolkit—Equips communities and local governments with materials to develop policies and practices to help prevent opioid-related overdoses and deaths, and addresses issues for first responders, treatment providers, and those recovering from opioid overdose.ⁱⁱ 	

ⁱ Available at: <http://www.drugabuse.gov/nidamed/etools>

ⁱⁱ Available at: <http://store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit/SMA13-4742>

Resources for Patients and Family Engagement

- **ACL:**
 - **Chronic Disease Self-Management Education Programs**—Provide education and tools to older adults and adults with disabilities to help them better manage chronic conditions including chronic pain.ⁱ
- **DEA:**
 - **National Take-Back Initiative**—Program gives patients a safe place to dispose of unused opioids.
- **FDA:**
 - **REMS**—Patient counseling document to guide education on risk and opioid management for patients on extended-release or on long-acting opioids.
- **VA:**
 - **“Taking Opioids Responsibly: For Your Safety and the Safety of Others”**—A patient education tool.

Resources To Promote Best Practices Within Communities

- **VA:**
 - **VHA National Pain Management Strategy**ⁱⁱ—Uses facility-level pain management committees to provide oversight and coordination of pain management activities to align care practices with the best practices.

Resources for Communication and Care Coordinationⁱⁱⁱ

- **AHRQ:**
 - **Project RED**—Includes a number of medication-related strategies (i.e., active medication reconciliation, medication teaching for patients and caregivers, development of medication list for patients and their health care providers).
- **DOD:**
 - **Sole Provider Program (SPP)**—Instituted by the Army as a risk mitigation program for high-risk patients, the SPP identifies high-risk patients and assigns a single provider and one alternate who are authorized to prescribe opioids.
- **IHS:**
 - **Nationally Clinical Pharmacy Specialists (NCPS) Program**^{iv}—Advanced pharmacy certification that allows for pharmacists to provide pain management at Gallup, NM; Anchorage, AK; and Claremore, OK.
 - Pharmacist-run pain management clinics with pharmacists prescribing medications, and ordering and interpreting labs per protocol.
- **VA:**
 - **Systems to track patient progress**—VA is piloting a mobile application for smartphones (VA Pain Coach) designed to provide tools to help patients set personal goals for pain management; track their symptoms, functioning, and self-care behaviors over time; and provide guidance on pain management strategies for patients and caregivers.
 - **Opioid Renewal Clinic at the Philadelphia VA Medical Center**—Primary care physicians refer at-risk patients to a pharmacist-run prescription management clinic, where an onsite pain nurse practitioner and a multispecialty pain team work together to stabilize the patient on an effective pain management plan before returning the patient to primary care management.

Abbreviations: CE = continuing education; DEA = Drug Enforcement Administration; REMS = Risk Evaluation and Mitigation Strategy; SPP = DOD Sole Provider Program; TMS = VA Talent Management System

ⁱ Available at: http://www.aoa.gov/AoARoot/AoA_Programs/HPW/ARRA/PPHF.aspx

ⁱⁱ Available at: http://www.va.gov/PAINMANAGEMENT/VHA_Pain_Management_Strategy.asp

ⁱⁱⁱ Available at: <http://www.cdc.gov/homeandrecreationalafety/overdose/research.html>

^{iv} Available at: http://www.usphs.gov/corpslinks/pharmacy/cpharm_creds.aspx

Inpatient Settings

In 2001, the Joint Commission developed standards for pain treatment to promote access to adequate pain management. In that context, The Joint Commission also identified opioids as an important cause of inpatient ADEs, with the most dangerous ADE being respiratory depression. The 2011 Joint Commission Sentinel Event Alert “Safe Use of Opioids in Hospitals” recommended improved assessment and management of pain to avoid accidental opioid overdose [20]. Accepted standards of care recommend a systematic approach to patient assessment and patient monitoring. Federal Agencies, including VA and DOD, have identified the following potential targets for reducing opioid ADEs: initiating patients on a high dose of opioids, converting between opioid formulations, and opioid dose titration. **Figure 21** outlines opportunities to advance ADE prevention strategies/tools in inpatient settings organized around the National Quality Strategy framework.

Figure 21. Opportunities for Advancing Opioid ADE Prevention Strategies/Tools, as Identified by the National Quality Strategy Priorities—Inpatient Settings

<p>Safer Care</p>	<ul style="list-style-type: none"> ▪ Expand dissemination of evidence-based opioid guidelines/ protocols (e.g., dosing changes, management of high-risk individuals)
<p>Patient and Family Engagement</p>	<ul style="list-style-type: none"> ▪ Promote patient education to improve the safety of care transition
<p>Effective Communication and Coordination of Care</p>	<ul style="list-style-type: none"> ▪ Develop more optimal and integrated health IT opioid management tools ▪ Coordinate care through practices such as medication reconciliation and discharge counseling
<p>Science-Driven Prevention and Treatment</p>	<ul style="list-style-type: none"> ▪ Promote systematic and coordinated care ▪ Promote safe practices at point of initiation of inpatient opioids ▪ Promote the use of evidence-based tools for morphine equivalent dose (MED) and transitions between formulations
<p>Promotion of Best Practices Within Communities</p>	<ul style="list-style-type: none"> ▪ Use metrics to monitor the use of opioid safety “best practices” ▪ Promote the use of evidence-based guidelines for monitoring

Abbreviations: MED = morphine equivalent dose

Outpatient Settings

Opioid ADEs in outpatient settings are a multifaceted problem. Although the ADE Action Plan does not directly address the issue of misuse/abuse, it does advocate for steps to improve prescribing behaviors

to prevent patients who are prescribed opioids from abusing opioids. Although the factors driving opioid overdoses are not completely understood, a number of factors have been associated with increased risk for opioid overdose in the outpatient setting, based on varying degrees of evidence, and can serve as targets for outpatient opioid overdose prevention. These risk factors are: concomitant use of central nervous system (CNS) depressants (especially benzodiazepines) [14, 20, 21], high daily opioid dose [22, 23, 24, 25, 26], recent initiation of opioid therapy in treatment-naive patients [20, 27, 28], multiple opioid prescribers [14, 29], mental health disorder co-morbidities [14, 20, 21, 28, 30], medical co-morbidities (e.g., sleep apnea) [3], active or history of substance abuse [20, 21, 28, 29], aberrant medication-related behaviors [14, 28, 31, 32], and higher risk formulations (e.g., methadone) [33]. Federal Agencies can play an essential role in promoting evidence-based strategies to address opioid overdose risk factors and promote safe practices. **Figure 22** presents opportunities to advance ADE prevention strategies/tools in outpatient settings organized around the National Quality Strategy Priorities.

Figure 22. Opportunities for Advancing Opioid ADE Prevention Strategies/Tools, as Identified by the National Quality Strategy Priorities—Outpatient Settings

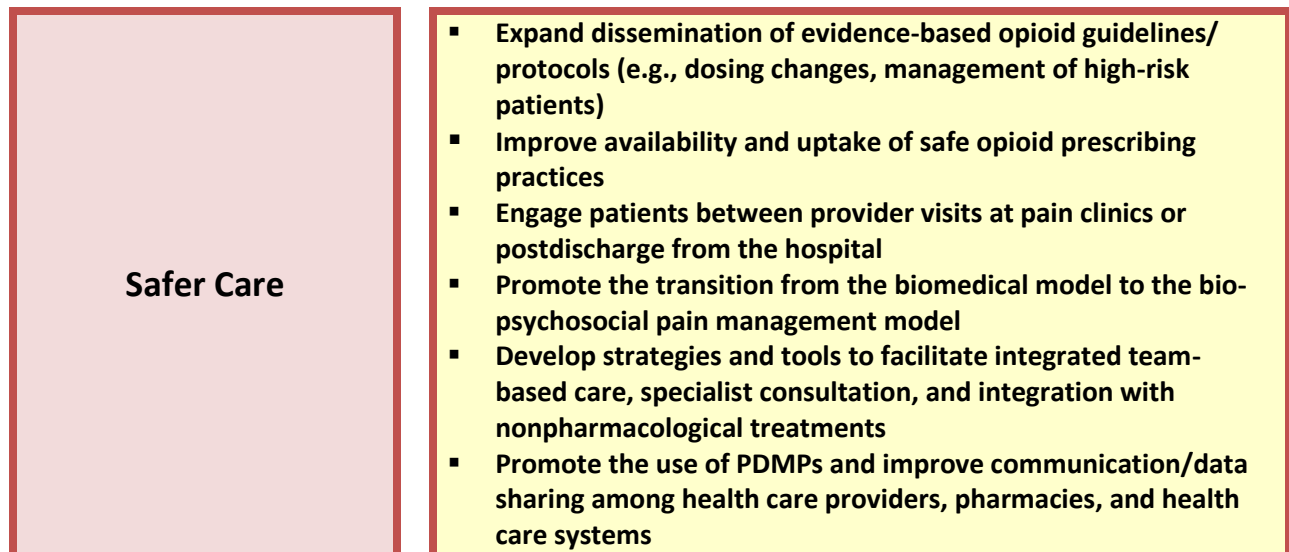


Figure 22. Opportunities for Advancing Opioid ADE Prevention Strategies/Tools, as Identified by the National Quality Strategy Priorities—Outpatient Settings (continued)

<p>Patient and Family Engagement</p>	<ul style="list-style-type: none"> ▪ Develop and distribute patient education materials and strategies, using the principles of health literacy and theories of behavioral change ▪ Spread public health messages promoting safe opioid storage, use, and disposal, and not sharing opioids with friends or family ▪ Educate patients and their families to recognize early signs of dependence
<p>Effective Communication and Coordination of Care</p>	<ul style="list-style-type: none"> ▪ Develop more optimal and integrated health IT opioid management tools ▪ Integrate opioid-specific targets into care transition models
<p>Science-Driven Prevention and Treatment</p>	<ul style="list-style-type: none"> ▪ Promote systematic and coordinated care through strategies such as team-based care and medication reconciliation ▪ Promote the use of evidence-based strategies for managing risk factors associated with opioid overdoses ▪ Increase availability of mental health and substance use disorder treatment for patients on opioid therapy ▪ Promote the use of health IT tools to identify high-risk opioid prescribing practices
<p>Promotion of Best Practices Within Communities</p>	<ul style="list-style-type: none"> ▪ Use metrics to monitor the use of opioid safety “best practices” ▪ Promote effective strategies identified by Federal Agencies that engage in patient care

Federal Agencies should explore ways to improve uptake of evidence-based strategies for safe opioid prescribing, including increased use of prescribing guidelines for chronic pain treatment and didactic provider training on opioid prescribing for both trainees and fully qualified clinicians (e.g., continuing education). More importantly, Federal Agencies should support training methods, interventions, and tools to encourage, model, and facilitate safe opioid prescribing.

Opioid prescribing guidelines for the treatment of chronic pain promote assessment of patient risk factors prior to initiating opioid therapy and recommend continued assessment of patient therapy goals and outcomes to determine the effectiveness and appropriateness of therapy. Prescribing guidelines also provide consensus-based strategies on how to reduce the risk for opioid ADEs. Knowledge of these strategies is necessary, although not sufficient for appropriate opioid prescribing; Federal Agencies should continue to work to educate clinicians on safe and appropriate opioid prescribing, and use available mechanisms to promote clinician education and effective behavior change. Federal Agencies

should work to develop, evaluate, and disseminate (1) training methods that include modeling, practice, expert collaboration, and/or feedback on real-patient cases (e.g., Project ECHO, Academic Detailing, expert consultation and mentoring); (2) interventions to identify and address high-risk cases (e.g., aberrant drug-related behavior or risk factor screening and intervention, high-risk patient treatment program, audit and feedback, or panel management systems); and (3) reminders and tools that guide clinicians in real time (e.g., computerized decision support systems, clinical reminders, dose determination tools).

Federal Agencies should promote patient-centered, multimodal, team-based care, from the health system level down to the clinician level, to personalize pain management, properly manage patients with high-risk medical and mental health co-morbidities, and intensively manage patients at high risk for opioid overdose.

Federal Agencies should promote evidence-based practices for pain management, including but not limited to opioid therapy. Federal Agencies should promote practices and services that identify and properly manage co-morbidities that increase the risk of opioid ADEs. This includes management of behavioral, mental health, and medical risk factors for unintentional and intentional opioid overdose and opioid abuse, as well as use of nonopioid pharmacological therapies and nonpharmacological therapies as part of an overall pain management plan. Currently, there is limited access to multimodal, evidence-based pain management and treatment of medical and psychiatric co-morbidities. Federal Agencies should promote access to evidence-based, multimodal, and interdisciplinary care for the management of chronic pain and co-morbidities. The Affordable Care Act provisions that support Mental Health parity may improve access to services that address mental health co-morbidities. Increased uptake of existing Health and Behavioral Assessment and Intervention CPT codes may also address this challenge.

Federal Agencies should develop and encourage the use of patient education materials and tools, in accordance with health literacy principles, to empower the patient to use opioids safely and encourage patient engagement.

Patients can play a major role in increasing the safe use of prescription opioids. To promote safe opioid use at home, patients should be educated about the safe and proper use of opioids for pain management, not sharing opioids, secure storage of opioids, and safe disposal of any opioids that are not used as part of therapy. Patient education materials, including materials the prescriber provides, should be developed using principles of health literacy to ensure that the patient understands the messages presented.

Patient education should also include ways to identify signs of misuse, abuse, dependence, and addiction, and to identify and treat an overdose. Federal Agencies should help develop, evaluate, and disseminate effective training, tools, and programs to provide patients with the skills and resources necessary to safely respond to moderate to severe pain and signs of misuse, abuse, and overdose, as well as to manage opioid therapy (e.g., medication take-back programs, overdose education and naloxone distribution programs, electronic tracking and reminder tools, suicide hotlines, and relaxation skills training).

Federal Agencies involved in patient care play an important role in assessing and promoting best practices for pain management and opioid safety.

BOP, DOD, IHS, and VA, all of which provide direct patient care, have taken steps to advance the practice of pain management and improve opioid safety. Because DOD and VA serve active-duty service members and military veterans who often have injuries requiring pain management, these agencies have been actively pursuing evidence-based pain management and systems to promote opioid safety.

Table 13 outlines the initiatives that are currently underway in VA and DOD systems and can be evaluated, modeled, and expanded to the private sector. DOD and VA have developed their own opioid prescribing guidelines for chronic pain [15] and have developed system-based methods to measure how the guidelines are followed and monitor trends associated with the use of opioid prescribing guidelines; however, prescriber adherence to the prescribing guidelines could be optimized with a system of continuous improvement. These agencies can serve as a model for the private sector as a system of continuous improvement and a system that promotes evidence-based pain management and evidence-based opioid ADE prevention strategies.

Table 13. Systematic Actions From VA and DOD Facilities for Safe and Effective Opioid Use for Pain Management

System	Action
Systematic Strategy	<ul style="list-style-type: none"> ▪ VA National Pain Management Strategy—Outlines systematic strategies to improve pain management while maintaining opioid safety. ▪ VA/DOD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain—Provides evidence-based recommendations on when and how to effectively and safely use opioids for chronic pain.
Performance Measurement	<ul style="list-style-type: none"> ▪ Structure measures—The VA Health Care Analysis and Information Group created and administered a survey assessing organization, policy, staffing, and availability of pain management services at health care facilities in 2010. ▪ Process measures—VA developed a set of administrative data-based metrics that assess facility-level adherence to key recommendations of the <i>VA/DOD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain</i>. ▪ Outcome measures—VA’s electronic Mental Health Assistant makes validated assessments for patient outcomes available for use in the EHR, including the Pain Outcomes Questionnaire (POQ), West Haven Yale Multidimensional Pain Inventory (WHYMPI), and the Brief Pain Inventory (BPI).
Point-of-Care Clinical Management and Information Support	<ul style="list-style-type: none"> ▪ VA’s ATHENA System—Opioid system is a point-of-care decision support system to guide opioid management. ▪ VA inpatient tools for converting among different strengths/formulations of opioids. ▪ VA’s Academic Detailing program uses clinical pharmacists and computerized panel management dashboards to work with primary care providers to address patient and clinical risk factors within their patient panel. ▪ VA’s Opioid Safety Initiative uses performance metric-based reviews and feedback to identify and assist providers with elevated rates of clinical risk factors within their patient caseload. ▪ VA’s SCAN-ECHO program links a community of primary care providers with pain specialists, using telehealth technology to provide co-management, consultation, and training on difficult patient cases.
Co-Morbidity Management/ Individualized Care	<ul style="list-style-type: none"> ▪ Mental Health Assessment and Treatment—VA requires annual screening for depression, using the Patient Health Questionnaire (PHQ-2), and for posttraumatic stress disorder (PTSD) using the Primary Care—PTSD (PC-PTSD) screen with referral for additional assessment and treatment of positive cases.

Abbreviations: BPI = Brief Pain Inventory; EHR = electronic health record; PHQ-2 = Patient Health Questionnaire; POQ = Pain Outcomes Questionnaire; PC-PTSD = Primary Care Posttraumatic Stress Disorder Screen; PTSD = posttraumatic stress disorder; SCAN-ECHO = Specialty Care Access Network—Extension for Community Healthcare Outcomes; WHYMPI = West Haven Yale Multidimensional Pain Inventory

Incentives and Oversight

Current work of Federal partners is important for monitoring administrative prescription data to identify high-risk prescribing practices and eliminate fraud, waste, and abuse related to opioids.

Prevention of Opioid Adverse Drug Events in Medicare Part D

Effective January 1, 2013, CMS implemented a new policy in Medicare Part D, requiring plan sponsors to better address potential overutilization of opioids in their prescription drug benefit plans through improved drug utilization controls and case management. The goal of this policy is for Part D sponsors to reduce the overutilization of opioids among their enrollees. The policy, described in the Contract Year (CY) 2013 Final Call Letter on April 2, 2012, with supplemental guidance issued on September 6, 2012, includes a medication safety-focused approach, while maintaining beneficiary access to needed medications. Through implementation of the Part D opioid policy, overutilization of opioids can be identified and addressed, and related ADEs may be reduced.

As part of their opioid overutilization programs, for cases not addressed through improved prospective formulary management, Part D sponsors are expected to use retrospective drug utilization reviews (DURs) to identify at-risk beneficiaries and engage in case management with their prescribers. The policy permits appropriate claim controls on coverage of opioids for identified enrollees, including safety edits and quantity limits applied at point of sale (POS), with prescriber agreement or when prescribers are not responsive to case management. The suggested retrospective DUR methodology to identify beneficiaries who are at the highest risk for opioid ADEs is based on cumulative daily morphine equivalent dose (MED) across all opioids used by the beneficiary for chronic pain and accounts for the beneficiary's use of multiple prescribers and pharmacies. The guidance also addresses data sharing among Part D plan sponsors when a beneficiary for whom an individual claim control has been implemented to prevent Part D coverage of unsafe dispensing of opioids, moves from one Part D plan to another.

CMS will monitor the implementation of the new opioid policy by Part D sponsors and perform an interim evaluation of its impact in 2014. Although not a requirement in the Final Call Letter for Contract Year 2014, CMS strongly encouraged all sponsors to consider developing the ability to implement drug-level POS edits based on cumulative MED across the opioid class as soon as possible.

State Medicaid Drug Monitoring for ADEs in the Fee-for-Service Outpatient Pharmacy Programⁱ

Pharmacy coverage is an optional benefit under Federal Medicaid law; however, all States currently provide coverage for outpatient prescription drugs to most enrollees within their Medicaid programs. The Medicaid prescription drug programs include the management, development, and administration of systems and data collection necessary to operate the Medicaid Drug Rebate program, the Federal Upper Limit calculation for generic drugs, and the DUR Program.

The Medicaid DUR Program promotes patient safety through State-administered utilization management tools and processes. The State Medicaid agency's electronic monitoring system screens prescription drug claims to identify problems, such as therapeutic duplication, drug–disease contraindications, incorrect dosage or duration of treatment, drug allergy, and clinical misuse or abuse, in order to minimize ADEs. DUR involves ongoing and periodic examination of claims data to identify patterns of medically unnecessary care and implements corrective action when needed.

Federal partners should expand monitoring of administrative prescription data to identify high-risk prescribing practices and eliminate fraud, waste, and abuse related to opioids.

Opportunities to advance the prevention of opioid ADEs through incentives and oversight-based strategies are summarized in **Figure 23**. Incentive and oversight levers that could advance opioid ADE prevention fall into three categories: (1) health care quality measures that are utilized in such programs as CMS value-based purchasing incentive programs (e.g., EHR Meaningful Use Incentive Program, Hospital Pay-for-Reporting, Inpatient Prospective Payment System); (2) reimbursement or coverage of services; and (3) identification of inappropriate opioid prescribing, fraud, and abuse through payor data. Although the FIW recommendations address the public payor perspective, the opportunities identified may also influence private sector advancements in this area, allowing for private payors to learn from successful public sector strategies.

ⁱ Detailed information on the Medicaid DUR program, along with reports the States submit annually on the operation of their programs can be found at: <http://medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Drug-Utilization-Review.html>

Figure 23. Federal Interagency Workgroup Recommendations for Actions That Can Potentially Advance Health Care Policy Strategies for Opioid ADE Prevention

Actions That Can Potentially Advance Health Care Policy Strategies for Preventing Opioid ADEs

Inpatient Settings

- Expand national health care quality reporting measures to include concepts related to multidisciplinary, systematic, and coordinated models of care.
- Develop and validate health care quality reporting measures that can be used to assess safe opioid prescribing and appropriate monitoring in the inpatient setting.

Outpatient Settings

- Address payment/coverage barriers to uptake of evidence-based, high-quality ADE prevention strategies and multimodal, team-based pain management.
- Expand national health care quality reporting measures to include ones *specific* to opioid ADE prevention through validated process measures that identify high-risk practices.
- Use administrative data from public and private payors and State PDMPs to identify high-risk patients and high-risk prescribers contributing to misuse/abuse and fraud.

Transitions of Care/Coordinated Care

- Address barriers to more integrated pain management.

Abbreviations: ADE = adverse drug event; PDMP= Prescription Drug Management Program

Health Information Technology (Health IT)

Federal Agencies that develop, promote, and incentivize EHR standards play an important role in advancing health IT-based strategies for inpatient opioid ADE prevention.

EHRs can serve an important role in providing patient-specific information that is necessary for making appropriate clinical decisions by providers. EHRs can also support the use of clinical decision support (CDS) to identify appropriate starting doses and MEDs between different opioid formulations to help clinicians safely transition between opioid formulations and identify appropriate doses. EHRs can also provide clinical reminders and templates to prompt and facilitate recommended clinical practices, and might improve assessment, documentation, and collaborative treatment planning for patient risk factors and aberrant behaviors.

The FIWs for ADEs proposed EHR (Stage 3) MU electronic clinical quality measures for EHRs that can potentially advance opioid ADE prevention.

Health care quality measures are important in helping to advance opioid ADE prevention efforts. In June 2013, the FIW for Opioid ADEs recommended a set of measure considerations to the Quality Measures Workgroup of the Health Information Technology Policy Committee. That committee, convened by the HHS ONC, makes recommendations for candidate measures for the Stage 3 EHR MU requirements. This will potentially support and advance opioid ADE prevention and monitoring for consideration in Stage 3 of the MU Incentive Program. These recommendations are summarized in **Table 14**. The recommendations are strictly for data collection purposes, to help clinicians and researchers gain a better understanding of the potential risk factors associated with opioid ADEs. There are currently no nationally endorsed metrics for opioid ADEs. As a result, the proposed recommendations were developed *de novo* or are based on VA-specific measures and require further development and validation as a tool for reducing opioid ADEs. After initial recommendation, measures under consideration are submitted to CMS for further review, development, and testing. Final measure acceptance is dependent on rigorous and complete internal and external public reviews.

The outpatient metrics detailed in **Table 14** targeted long-term opioid use for chronic pain and are modeled after measures that are currently in use by VA to measure adherence to the *VA/DOD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain*.

Table 14. Measure Considerations for EHR (Stage 3) MU Requirements That Can Potentially Advance Opioid ADE Prevention, as Proposed by the Federal Interagency Workgroup for Opioid ADEs

Metric	Description and Justification
Outpatient Clinical Quality Measure Concepts	
Patients on high daily dose of long-term opioid therapy	<ul style="list-style-type: none"> There is an association between high daily dose of opioids and opioid ADEs, which requires further study to understand the impact on clinical practice.
Patients co-prescribed long-term opioid therapy and CNS depressants	<ul style="list-style-type: none"> Co-prescribing of opioids with CNS depressants, especially benzodiazepines, is associated with opioid overdose deaths.
Patients on long-term opioid therapy given a toxicology screen prior to initiating therapy and at least once a year while on long-term opioid therapy	<ul style="list-style-type: none"> All guidelines recommend assessment of risk related to substance abuse prior to initiating opioids and while patients are on therapy.
Patients on long-term opioid therapy who were checked in to the relevant Prescription Drug Monitoring Program prior to initiating therapy and at least every year if on chronic opioid therapy	<ul style="list-style-type: none"> Guidelines recommend monitoring PDMPs when available. Early data show that PDMPs may be effective, although more research will be necessary as PDMPs continue to be developed and used.
Patients on long-term opioid therapy who have evidence of a written opioid care management plan	<ul style="list-style-type: none"> All guidelines recommend that patients starting on long-term opioid therapy have an opioid care management plan that identifies the goals of therapy and the expectations for the patient.
Number of patients on long-term opioid therapy who have evidence of mental health assessment	<ul style="list-style-type: none"> All guidelines recommend assessment for mental health disorders prior to initiating opioids, and treatment as appropriate.
Number of patients in facility or practice prescribed opioids	<ul style="list-style-type: none"> Numbers are based on a VA measure that is used to compare prescribing rates across facilities.
Inpatient Clinical Quality Measure Concepts	
Opioid-naïve patients started on high-dose opioids in the inpatient setting	<ul style="list-style-type: none"> Inappropriate prescribing is a significant problem that can lead to opioid overdose in the inpatient setting, especially in high-potency formulations.
Clinical Decision Support (CDS) Rule Concepts	
Clinical decision support rules to support all measure concepts	<ul style="list-style-type: none"> There should be supporting clinical decision support to promote best practices and improve measured processes.

Abbreviations: ADE = adverse drug event; CNS = central nervous system; IV = intravenous; PCA = patient-controlled analgesia; PDMP = Prescription Drug Monitoring Program

Research (Unanswered Questions)

There remain a number of unanswered questions related to the prevention of opioid ADEs. As a result, there is a great opportunity for impact through research. Federal resources can play a pivotal role in

addressing research questions that can advance opioid safety and improve overall pain management. These are summarized in **Figure 24**.

Figure 24. Federal Interagency Workgroup Recommendations for Actions That Can Potentially Advance Research Strategies for Opioid ADE Prevention

Actions That Can Potentially Advance Research Areas for Opioid Safety

Clinical Science Domain

(CDC, AHRQ, FDA, NIH, public–private sector collaborations)

- Evaluate the effectiveness of prevention strategies (e.g., UDS, maximum doses, opioid agreements, single opioid prescriber) that are recommended in opioid prescribing guidelines.
- Improve standardization and coordination of surveillance systems addressing opioid ADEs.
- Promote standardized definitions/criteria for aberrant behavior, misuse, abuse, and adverse events to compare results across studies, settings, and health systems.
- Study real-world management of patients identified as high risk for opioid ADEs (e.g., promote the establishment and use of voluntary patient registries).
- Evaluate the clinical outcomes of using PDMPs and the effects on prescribers and patients.
- Develop strategies to better coordinate care and improve data sharing between settings.

Clinical/Laboratory/Bench-Top Science Domain

(CDC, NIH, public–private sector collaborations)

- Research biochemical and genetic mechanisms for the etiology of chronic pain.
- Fund and coordinate a comprehensive evaluation of the safety and efficacy of long-term opioid therapy for chronic pain through high-quality randomized controlled clinical trials supplemented by data collected from clinical care.
- Research risk factors associated with ADEs to define high-risk prescribing practices and identify patients at risk for opioid ADEs.
- Examine emerging pharmacogenomics related to hypermetabolizers of opioids.
- Pursue innovative drug development for abuse resistant opioid formulations and nonopioid drugs for refractory pain.
- Evaluate the effectiveness of and adopt adjunctive and behavioral modalities that augment pain therapy and reduce opioid use for chronic pain.

Abbreviations: ADE = adverse drug event; PDMP = Prescription Drug Monitoring Program; UDS = urine drug screen

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Conclusions and Next Steps

Despite decades of attention on improving patient safety, adverse drug events (ADEs) remain an important, but largely preventable, source of harm to patients wherever they encounter the health care system, including inpatient, outpatient, and long-term care settings. The process of developing the *National Action Plan for Adverse Drug Event Prevention* has facilitated communication and collaborations across the U.S. Department of Health and Human Services (HHS) and other Federal partners around this critical public health and patient safety issue. Through the Federal Interagency Steering Committee and Workgroups, Federal Agencies have shared existing tools, resources, and best practices for defining, measuring, tracking, and preventing ADEs, and have also identified challenges and opportunities in advancing the field of ADE prevention.

The ADE Action Plan is only the first step in more systematic efforts by Federal partners to address surveillance, prevention, policies, and research around high-priority ADE targets in an aligned and coordinated fashion across the Federal Government. As a followup to the ADE Action Plan, it will be critical that Federal partners initiate collaborations with other public and private stakeholders. It is hoped that increased Federal attention to the high prevalence of ADEs and their negative impact on patients, providers, and health care costs will improve awareness and support for these efforts across public and private sectors. Broadly, the ADE Action Plan has identified Federal assets that could be leveraged in the following areas:

- **Surveillance**—Use of enhanced and more consistent definitions of ADEs, specifically those associated with high-priority ADE targets (i.e., anticoagulants, diabetes agents, opioids), to allow for more effective measuring and tracking of ADEs.
- **Prevention**—Support of development, dissemination, and uptake of evidence-based guidelines, best practices, tools, and provider and patient education resources that are specific to high-priority ADE targets, particularly among high-risk patient populations (e.g., older adults) and in high-risk settings, where ADE prevention strategies may be lacking (e.g., care transitions, long-term care)
- **Incentives and Oversight**—Support of policies and quality improvement efforts through current and future health care quality measures, and payment programs and models.

- **Research**—Support of ongoing research and evaluations that can help inform efforts to identify patients at highest risk of ADEs, and of the most effective ADE prevention strategies.

In addition, more coordinated and focused use of health information technology will play a critical role in advancing ADE prevention efforts through various mechanisms, including but not limited to improvements in detection and monitoring of ADEs on the basis of more integrated and accessible electronic health record (EHR) data, electronic transfer of medication information across multiple providers and multiple settings, facilitating improvements in linkages between pertinent pharmacy and laboratory data, and integration of clinical decision support tools and health care quality measures specifically targeting high-priority ADEs.

The success of the ADE Action Plan will depend on ongoing coordination and collaboration across the Federal Government and among Government Agencies, national experts, and key public and private stakeholders. The ADE Action Plan should serve as a catalyst to promote leaders at the Federal, State, and local levels to implement evidence-based guidelines and engage in strategies that will help advance the goals of the ADE Action Plan. If the national burden of ADEs is to be reduced, Federal partners must continue in their coordinated and aligned efforts toward this shared goal, providers must be afforded every opportunity to safely and effectively manage medications, and patients must be enabled to become educated, engaged consumers and partners in their health care.

In future years, as progress is made in reducing ADEs from the initial targets of the ADE Action Plan (i.e., anticoagulants, diabetes agents, opioids), efforts will need to be retooled to additional and newly emerging medication safety targets. In addition, the ADE Action Plan will need to be adapted to reflect evolving science and technology.

In the meantime, HHS will continue the activities initiated in developing the ADE Action Plan, including

- Facilitating and coordinating nationwide and State-based efforts to align and enhance ADE surveillance and prevention
- Coordinating quarterly meetings of the Federal Interagency Steering Committee for ADEs to share current Federal efforts related to ADE prevention
- Investigating opportunities to host a public meeting focused on sharing and disseminating current and future best practices, policies, and research around ADE surveillance and prevention

- Leveraging a cross-cutting Federal communication workgroup to conduct outreach and education to public and private stakeholders around ADEs
- Supporting continued investment in research to inform and advance medication safety
- Identifying opportunities to incorporate measures related to high-priority ADE targets into existing and future CMS programs
- Identifying specific quantitative targets, measurable metrics, and analysis methodology to assess the impact of the *National Action Plan for Adverse Drug Event Prevention* following its implementation (as improvements in surveillance allow for more effective tracking of ADEs)

By leveraging the extensive experience of HHS and other Federal partners in improving the health and welfare of Americans, we are confident that the goals outlined in the *National Action Plan for Adverse Drug Event Prevention* will help advance overall patient safety and wellness across the Nation.

APPENDIX

A

Key Partnerships in Development of the National ADE Action Plan

Table A–1. Roles and Activities of U.S. Department of Health and Human Services (HHS) Operating Divisions and Other Federal Agencies Involved in Development of the National Action Plan for ADE Prevention

HHS Operating Division/ Federal Agency	Role/Activity
Bureau of Prisons	
BOP	<ul style="list-style-type: none"> Provides medical, dental, and mental health to Federal inmates in Bureau facilities, including health care delivery, infectious disease management, and medical designations.
Department of Defense	
DOD	<ul style="list-style-type: none"> Ensures health care to active duty members, retired service members, National Guard/Reserve members, families, survivors, and others entitled to DOD medical care.
Department of Health and Human Services	
AHRQ	<ul style="list-style-type: none"> Supports research to identify root causes of threats to patient safety, inform decisions, and improve the quality of health care services. Manages systems to collect patient safety data.
ACL	<ul style="list-style-type: none"> Provides resources/programs to support care coordination and consumer and caregiver activation.
CDC	<ul style="list-style-type: none"> Conducts national surveillance to identify magnitude of and risk factors for health care-related harms. Collaborates with partners to identify effective prevention strategies and provide public health leadership.
CMS	<ul style="list-style-type: none"> Leverages payment policies and data transparency to enhance delivery of quality care. Implements traditional and innovative quality improvement programs.

Table A–1. Roles and Activities of U.S. Department of Health and Human Services (HHS) Operating Divisions and Other Federal Agencies Involved in Development of the National Action Plan for ADE Prevention (continued)

HHS Operating Division/Federal Agency	Role/Activity
Department of Health and Human Services (continued)	
FDA	<ul style="list-style-type: none"> ▪ Involved in risk mitigation. ▪ Supports ADE surveillance.
HRSA	<ul style="list-style-type: none"> ▪ Improves health and achieves health equity of uninsured, isolated, and medically vulnerable populations through access to quality services, a skilled health workforce and innovative programs.
IHS	<ul style="list-style-type: none"> ▪ Ensures that comprehensive, culturally acceptable personal and public health services are available and accessible to American Indian and Alaska Native people.
NIH	<ul style="list-style-type: none"> ▪ Conducts and supports research into the causes, diagnosis, prevention, and cure of human diseases, and in directing programs for the collection, dissemination, and exchange of information in medicine and health.
OS/ASPE	<ul style="list-style-type: none"> ▪ Advises on policy development, and is responsible for major activities in policy coordination, legislation development, strategic planning, policy research, evaluation, and economic analysis.
OS/ONC	<ul style="list-style-type: none"> ▪ Supports the adoption of health information technology and the promotion of nationwide health information exchange to improve health care.
SAMHSA	<ul style="list-style-type: none"> ▪ Provides information, education, and outreach on medication misuse/abuse.
Department of Veterans Affairs	
VA	<ul style="list-style-type: none"> ▪ Provides health care to eligible Veterans, partners with other Federal departments and Agencies to measure the frequency and impact of ADEs. ▪ Supports surveillance.

Abbreviations: AHRQ = Agency for Healthcare Research and Quality; ACL = Administration for Community Living; ASPE = Assistant Secretary for Planning and Evaluation; BOP = Bureau of Prisons; CDC = Centers for Disease Control and Prevention; CMS = Centers for Medicare & Medicaid Services; DOD = Department of Defense; FDA = Food and Drug Administration; HRSA = Health Resources and Services Administration; IHS = Indian Health Services; NIH = National Institutes of Health; ONC = Office of the National Coordinator for Health IT; OS = Office of the Secretary; VA = U.S. Department of Veterans Affairs

APPENDIX B

Overview of Federal Systems That Conduct ADE Surveillance

Table B–1. Federal Systems for Conducting ADE Surveillance—National Surveillance Systems

Agency	AHRQ	AHRQ	AHRQ	CDC	FDA	FDA
System Name	HCUP-Nationwide Inpatient Sample (NIS); State Inpatient Databases	HCUP-NEDS	MPSMS*	NEISS-CADES	FAERS	Sentinel Initiative Mini-Sentinel Pilot
Active or Passive?	Active	Active	Active	Active	Passive (voluntary)	Active
Surveillance Population	Patients in U.S. short-term, acute-care, non-Federal hospitals	Visits to U.S. emergency departments in short-term, acute care, non-Federal hospitals	U.S. (all payors)	Visits to U.S. emergency departments in short-term, acute-care hospitals	U.S. and Foreign	Enrollees in 18 large health plans including: (currently) Aetna, HealthCore, Humana, Optum, HMORN (partial) Kaiser (partial), Vanderbilt University (TN, WI Medicaid data)
System Focus	Research and statistical reporting on utilization and costs of care provided in U.S. hospitals	Research and statistical reporting on utilization and costs of care provided in U.S. emergency departments	Hospital complications from select medications (e.g., anticoagulants, insulin, digoxin)	Monitoring acute harms from commonly used medications in ambulatory care	Signal detection and assessment	Signal assessment

Table B–1. Federal Systems for Conducting ADE Surveillance—National Surveillance Systems (continued)

Agency	AHRQ	AHRQ	AHRQ	CDC	FDA	FDA
Setting of Drug Exposure	Inpatient or outpatient (can distinguish between exposure setting when the data system provides information on whether diagnoses were present on admission [POA]—this information is available for a subset of States contributing to HCUP)	Emergency department (no POA information is provided for ED visits)	Select adult inpatient populations (those with hospital discharge diagnosis of HF, AMI, or pneumonia)	Outpatient (all ages)	All settings	Drug exposure in any setting <ul style="list-style-type: none"> ▪ Inpatient (including, procedures) ▪ Outpatient (including, procedures)
Geographic Scope	<ul style="list-style-type: none"> ▪ National (~1,000 hospitals) ▪ Regional stratification ▪ State estimates for some States 	<ul style="list-style-type: none"> ▪ National (~1,000 hospitals) ▪ Regional stratification ▪ State estimates for some States 	<ul style="list-style-type: none"> ▪ National (~800 of ~3,400 hospitals) ▪ No regional stratification 	<ul style="list-style-type: none"> ▪ National (~63 hospitals) ▪ No regional stratification 	Foreign and domestic	Varying with data partners/sources; Currently Sentinel covers > 125 million lives (does not constitute a nationally representative sample)
Data Source(s)	Hospital billing data	ED billing data	Hospital discharge medical records	ED medical records	<ul style="list-style-type: none"> ▪ (Primarily) post-marketing, spontaneous AE reports ▪ (Some) clinical trial AE reports 	<ul style="list-style-type: none"> ▪ Insurance claims ▪ Public and private administrative claims

Table B–1. Federal Systems for Conducting ADE Surveillance—National Surveillance Systems (continued)

Agency	AHRQ	AHRQ	AHRQ	CDC	FDA	FDA
Data Collection Method	<ul style="list-style-type: none"> NIS is a stratified sample of about 1,000 hospitals; all discharge records (~8 million) are retained in the dataset. SIDs are based on discharge data collected by statewide data organizations and shared with AHRQ through voluntary agreements. 	NEDS is based on ED data collected by statewide data organizations and shared with AHRQ through voluntary agreements. NEDS is a stratified sample of about 1,000 hospital-based EDs; all records of stays (~25—30 million) are retained in the dataset.	Random national sample	National stratified probability sample	Voluntarily submitted reports	Database queries
Case Identification Method	<ul style="list-style-type: none"> Algorithmic detection using ICD-9-CM codes 	<ul style="list-style-type: none"> Algorithmic detection using ICD-9-CM codes 	Algorithmic detection based on chart abstraction of <i>select</i> ADEs (select anticoagulants, antibiotic-related CDI, insulin, oral diabetes agents, digoxin)	Algorithmic detection based on chart abstraction using clinician diagnosis as it appears in medical record narrative (not ICD-9-CM coding)	MedDRA Preferred Terms (PTs) or Standardized MedDRA Queries (SMQs)	Algorithm detection using drug exposure codes (dispensing), ICD-9-CM codes (diagnosis), and CPT (procedure) codes

* In 2015, MSPMS will be replaced by the Quality and Safety Review System (QSRS) for Health Systems, and AHRQ Common Formats utilized as the primary data collection method.

Table B–2. Federal Systems for Conducting ADE Surveillance—Federal Health Systems

Agency	BOP	DOD	DOD	IHS	VHA	VHA
System Name	N/A	Pharmacovigilance Defense Application System	Patient Safety Reporting System	Resource and Patient Management System (RPMS-EHR)	VA ADERs	Department of VA Integrated Databases
Active or Passive?	Passive (voluntary)	Active	Passive (voluntary)	Passive (voluntary)	Passive (voluntary)	Active
Surveillance Population	Inmates in facilities under the supervision of BOP	DOD (active duty, family members and retirees and family members)	DOD (active duty, family members and retirees and family members)	Federally recognized American Indians and Alaska Natives	VHA	VHA
System Focus	Quality improvement	<ul style="list-style-type: none"> ▪ Signal generation ▪ Signal refinement ▪ Signal evaluation ▪ Quality improvement 	<ul style="list-style-type: none"> ▪ Signal detection ▪ Quality improvement 	<ul style="list-style-type: none"> ▪ Signal detection ▪ Quality improvement ▪ Patient care 	<ul style="list-style-type: none"> ▪ Signal detection ▪ Quality improvement 	<ul style="list-style-type: none"> ▪ Signal detection ▪ Quality improvement
Setting of Drug Exposure	<ul style="list-style-type: none"> ▪ Inpatient ▪ Outpatient 	<ul style="list-style-type: none"> ▪ Inpatient (all ages) ▪ Outpatient (all ages) 	<ul style="list-style-type: none"> ▪ Inpatient (military treatment facilities) ▪ Outpatient (military treatment facilities) 	<ul style="list-style-type: none"> ▪ Inpatient ▪ Outpatient 	<ul style="list-style-type: none"> ▪ Inpatient (VHA facilities) ▪ Outpatient (VHA facilities) 	<ul style="list-style-type: none"> ▪ Inpatient ▪ Outpatient
Geographic Scope	<ul style="list-style-type: none"> ▪ Regional BOP ▪ Facility 	<ul style="list-style-type: none"> ▪ National DOD ▪ Facility ▪ Service 	<ul style="list-style-type: none"> ▪ National DOD-run facilities ▪ Facility level ▪ Service level 	<ul style="list-style-type: none"> ▪ National IHS ▪ Regional area office ▪ Facility ▪ Individual patient care 	<ul style="list-style-type: none"> ▪ National VHA ▪ Regional VHA ▪ VHA network ▪ Facility 	<ul style="list-style-type: none"> ▪ National VHA ▪ Regional VHA ▪ VHA network ▪ Facility

Table B–2. Federal Systems for Conducting ADE Surveillance—Federal Health Systems (continued)

Agency	BOP	DOD	DOD	IHS	VHA	VHA
Data Source(s)	Spontaneous AE reports	<ul style="list-style-type: none"> ▪ DOD EHRs ▪ DOD administrative claims 	Patient Safety Reporting System Submitted Reports	<ul style="list-style-type: none"> ▪ RPMS-EHR ▪ Adverse Reaction Tracking System ▪ Administrative datasets (Webcident) 	<ul style="list-style-type: none"> ▪ Spontaneous AE reports 	<ul style="list-style-type: none"> ▪ VHA EHRs ▪ VHA administrative claims
Data Collection Method	EHR review	Database queries (automated and ad hoc; updated quarterly)	Electronically submitted reports	Database queries	Database queries	Database queries
Case Identification Method	Review of cases with prescribed medication (anticoagulants)	<ul style="list-style-type: none"> ▪ Algorithmic detection using combination of drug exposure/J-code and ICD-9-CM/ CPT, LOINC codes ▪ Clinic visits, ED visits, hospitalizations, and procedures following drug exposure 	Patient Safety Reporting System collections on both ADE and ADRs.* ADE are classified as: death, severe permanent harm, temporary harm, additional treatment, emotional distress or inconvenience, no harm, near miss (did not reach patient), unsafe condition	<ul style="list-style-type: none"> ▪ Algorithmic detection using ICD-9-CM codes ▪ Clinic visits, ED visits, hospitalizations following drug exposure 	MedDRA codes	<ul style="list-style-type: none"> ▪ Algorithmic detection using ICD-9-CM codes ▪ Clinic visits, ED visits, and hospitalizations following drug exposure

* Adverse drug reaction (ADR): A subtype of an ADE that stems directly from taking an appropriate dose of the drug. ADEs also may be caused by a medication error, intentional overdose, or other inappropriate use (of an otherwise appropriate drug).

Abbreviations

ADE	adverse drug event
AE	adverse event
AMI	acute myocardial infarction
AHRQ	Agency for Healthcare Research and Quality
BOP	Bureau of Prisons
CDC	Centers for Disease Control and Prevention
CDI	Clostridium difficile infection
CPT	Current Procedural Terminology
DOD	Department of Defense
ED	emergency department
EHR	electronic health record
FDA	Food and Drug Administration
FAERS	FDA Adverse Event Reporting System
HCUP-NEDS	Healthcare Cost and Utilization Project—Nationwide Emergency Department Sample
HCUP-NIS	Healthcare Cost and Utilization Project—Nationwide Inpatient Sample
HF	heart failure
ICD-9-CM	International Classification of Diseases (ICD), Ninth Revision, Clinical Modification
IHS	Indian Health Service
LOINC	Logical Observation Identifiers Names and Codes
MPSMS	Medicare Patient Safety Monitoring System
NEISS-CADES	National Electronic Injury Surveillance System—Cooperative Adverse Drug Events Surveillance System
POA	present on admission
PTs	MedDRA Preferred Terms
RPMS	Resource and Patient Management System
SID	State Inpatient Database
SMQs	Standardized MedDRA Queries
VA ADERs	VA Adverse Drug Event Database
VHA	Veterans Health Administration

APPENDIX
C

Affordable Care Act Health Care Delivery Models Relevant to ADE Prevention

Table C–1. Affordable Care Act Health Care Delivery Models Relevant to ADE Prevention

Term	Definition
Patient-centered medical home (PCMH)	<p>Patient-centered medical home is a care delivery model designed to improve quality of care through better coordination, treating the many needs of the patient at once, increasing access, and empowering the patient to be a partner in his/her own care. Central attributes of PCMH models of care include enhanced patient access to a regular source of primary care; stable and ongoing relationships with a personal clinician who directs a care team; and timely, well-organized health services that emphasize prevention and chronic care management. An important feature of medical homes is enhanced payment in recognition of the infrastructure needed to provide more services.</p> <p>Evidence suggests that, on the whole, PCMHs improve patient experiences and outcomes by increasing access to care, encouraging the receipt of recommended preventive services, and facilitating better management of chronic conditions.</p> <p>Source: Davis K et al. How the Affordable Care Act Will Strengthen the Nation’s Primary Care Foundation. 2011. J Gen Intern Med, 26(10): 1201–1203.</p>
Accountable Care Organization (ACO)	<p>An ACO refers to a group of providers and suppliers of services (e.g., hospitals, physicians, and others involved in patient care) that will work together to coordinate care for the patients they serve with Original Medicare (that is, those who are not in a Medicare Advantage private plan). The goal of an ACO is to deliver seamless, high-quality care for Medicare beneficiaries. The ACO would be a patient-centered organization in which the patient and providers are true partners in care decisions.</p> <p>The Affordable Care Act specifies that an ACO may include the following types of groups of providers and suppliers of Medicare-covered services:</p> <ul style="list-style-type: none"> ▪ ACO professionals (i.e., physicians and other practitioners meeting the statutory definition) in group practice arrangements ▪ Networks of individual practices of ACO professionals ▪ Partnerships or joint venture arrangements between hospitals and ACO professionals ▪ Hospitals employing ACO professionals ▪ Other Medicare providers and suppliers, as determined by the Secretary <p>Source: Centers for Medicare & Medicaid Services. Medicare Learning Network. Summary of Final Rule Provisions for Accountable Care Organizations under the Medicare Shared Savings Program. Available at: http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/sharedsavingsprogram/Downloads/ACO_Summary_Factsheet_ICN907404.pdf. Accessed January 7, 2014.</p>

Table C–1. Affordable Care Act Health Care Delivery Models Relevant to ADE Prevention (continued)

Term	Definition
Team-based health care	<p>Implemented through ACOs and can be defined as: The provision of health services to individuals, families, and/or their communities by at least two health providers who work collaboratively with patients and their caregivers to the extent preferred by each patient—to accomplish shared goals within and across settings to achieve coordinated, high-quality care.</p> <p>Source: Mitchell P, Wynia M, Golden R et al. Core Principles & Values of Effective Team-Based Health Care. Institute of Medicine of the National Academies. Available at: http://www.iom.edu/global/perspectives/2012/teambasedcare.aspx. Accessed January 7, 2014.</p>

APPENDIX

D

Overview of CMS Programs/Initiatives With Potential To Advance ADE Prevention

Table D–1. Overview of CMS Programs and Initiatives That Support ADE Prevention

Program/Initiative	Description	General ADEs Addressed	ADE Targets (Anticoagulants, Diabetes Agents, Opioids) Specifically Addressed?	Opportunities
Regulatory Oversight				
Conditions of Participation (CoPs), Conditions for Coverage (CfCs), and long-term care facility (LTCF) requirements	<ul style="list-style-type: none"> Federal health and safety requirements for hospitals and other providers and suppliers All Medicare- and Medicaid-participating providers to be in compliance 	<p><i>Hospital CoPs</i></p> <ul style="list-style-type: none"> Policies/procedures to minimize errors related to drugs Report errors Require internal process to track adverse events (including ADEs), analyze cause, and implement preventive actions <p><i>Critical Access Hospital CoPs</i></p> <ul style="list-style-type: none"> Report adverse drug and drug administration errors <p><i>Long-Term Care CoPs</i></p> <ul style="list-style-type: none"> Free of medication errors >5% Free of ALL significant medication errors Drug regimens not include unnecessary drugs <p><i>Home Health Agency CoPs</i></p> <ul style="list-style-type: none"> Drug regimen review Focus on adverse effects, drug interactions, duplicate drugs, noncompliance 	<p><i>Long-term Care</i></p> <ul style="list-style-type: none"> Specific use/guidelines for <ul style="list-style-type: none"> Anticoagulants Diabetes agents Opioids 	Opportunity for improving ADE prevention practices

Table D–1. Overview of CMS Programs and Initiatives That Support ADE Prevention (continued)

Program/Initiative	Description	General ADEs Addressed	ADE Targets (Anticoagulants, Diabetes Agents, Opioids) Specifically Addressed?	Opportunities
Regulatory Oversight				
Survey & Certification	<ul style="list-style-type: none"> Assess compliance with CoPs and CfCs 	<ul style="list-style-type: none"> Guidelines and policy memos related to prevention of ADEs 	No	Opportunity for improving ADE prevention practices
Value-Based Purchasing Financial Incentives				
Hospital Inpatient Quality Reporting Program	<ul style="list-style-type: none"> Hospitals required to report quality measures or subject to payment reduction Measures are publicly reported on CMS Web site 	No	No	Opportunity for development of quality measures specific to the ADE targets
Value-Based Purchasing Financial Incentives				
Physician Quality Reporting System	<ul style="list-style-type: none"> Eligible professionals receive incentive payment for meeting satisfactory reporting criteria for quality measures. Beginning in 2015, eligible professionals who do not meet satisfactory reporting criteria of quality measures will be subject to payment adjustment. 	Measure #46—Medication Reconciliation Measure #130—Documentation of Current Medications in the Medical Record Measure #176—Rheumatoid Arthritis: Tuberculosis Screening Measure #238—Use of High-Risk Medications in the Elderly Measure #271—Inflammatory Bowel Disease: Preventive Care: Corticosteroid-Related Iatrogenic Injury—Bone Loss Assessment	Measure #380—ADE Prevention and Monitoring: Warfarin Time in Therapeutic Range	Opportunity for development of quality measures specific to the ADE targets

Table D–1. Overview of CMS Programs and Initiatives That Support ADE Prevention (continued)

Program/Initiative	Description	General ADEs Addressed	ADE Targets (Anticoagulants, Diabetes Agents, Opioids) Specifically Addressed?	Opportunities
		Measure #274—Inflammatory Bowel Disease: Testing for Latent Tuberculosis Before Initiating Anti-Tumor Necrosis Factor Therapy Measure #275—Inflammatory Bowel Disease: Assessment of Hepatitis B Virus Status Before Initiating Anti-Tumor Necrosis Factor Therapy Measure #337—Tuberculosis Prevention for Psoriasis and Psoriatic Arthritis Patients on a Biological Immune Response Modifier		
Hospital-Based Value Purchasing	<ul style="list-style-type: none"> ▪ Increased payment for hospitals demonstrating high quality ▪ Penalties for hospitals demonstrating poor quality 	No	No	Opportunity to include ADE measures in future years
Value-Based Purchasing Financial Incentives				
Medicare and Medicaid Electronic Health Record (EHR) Incentive Programs	<ul style="list-style-type: none"> ▪ Incentive payments for hospitals and eligible professionals that demonstrate meaningful use of a certified EHR technology 	<ul style="list-style-type: none"> ▪ Providers must maintain active medication list, implement drug–drug and drug–allergy interaction checks, and implement clinical decision support rules. ▪ EHR Stage 2 Meaningful Use Clinical Quality Measure: Use of high-risk medications in older adults ▪ Use of high-risk medications in older adults 	<ul style="list-style-type: none"> ▪ Specific clinical quality measures related to ADEs: <ul style="list-style-type: none"> – Warfarin Time in Therapeutic Range VTE discharge instructions for patients on warfarin 	Opportunity for incorporation of quality measures specific to the ADE targets as part of EHR requirements and tools (e.g., Clinical Decision Support)

Table D–1. Overview of CMS Programs and Initiatives That Support ADE Prevention (continued)

Program/Initiative	Description	General ADEs Addressed	ADE Targets (Anticoagulants, Diabetes Agents, Opioids) Specifically Addressed?	Opportunities
Physician Feedback Program and Value-Based Payment Modifier	<ul style="list-style-type: none"> ▪ Produce annual physician feedback reports ▪ Physician Fee Schedule payment modified based on quality of care compared with costs 	No	No	Opportunity for development of quality measures specific to the ADE targets
Value-Based Purchasing Financial Incentives				
Health Care Innovation Awards	<ul style="list-style-type: none"> ▪ Supports organizations using new ideas to enhance quality and reduce cost to Medicare, Medicaid, CHIP recipients. 	<ul style="list-style-type: none"> ▪ 47 projects provide medication reconciliation or management services. 	No	Opportunities to address ADEs in future rounds of funding
Pioneer Accountable Care Organizations (ACOs)	<ul style="list-style-type: none"> ▪ Shared savings payment model focusing on population-based health 	<ul style="list-style-type: none"> ▪ Many ACOs have participated in efforts to enhance drug safety, including use of barcoding, computerized provider order entry (CPOE), medicine decision support, public reporting. 	No	Opportunities to enhance Pioneer ACO efforts to reduce ADEs
Multi-Payer Advanced Primary Care Practice	<ul style="list-style-type: none"> ▪ State-level multi-payer reforms to expand advanced primary care practices ▪ Primary Care Medical Homes (PCMHs) receive monthly care management fees for Medicare. 	<ul style="list-style-type: none"> ▪ Two States focus on medication safety through clinical pharmacy, case management, efforts to reduce medication errors and complications, use of electronic data system for managing pharmacy care. 	No	Opportunities to expand ADE efforts into additional States

Table D–1. Overview of CMS Programs and Initiatives That Support ADE Prevention (continued)

Program/Initiative	Description	General ADEs Addressed	ADE Targets (Anticoagulants, Diabetes Agents, Opioids) Specifically Addressed?	Opportunities
Community-Based Care Transitions Program	<ul style="list-style-type: none"> ▪ Models to improve care transitions ▪ Goals: reduce readmissions, improve quality, save cost 	<ul style="list-style-type: none"> ▪ All sites provide medication reconciliation. 	No	Opportunities to enhance focus on ADEs
Transparency and Associated Incentives				
Hospital Compare	<ul style="list-style-type: none"> ▪ Consumer-oriented Web site providing information on hospital quality 	<ul style="list-style-type: none"> ▪ Some hospitals voluntarily report data on ADEs. 	No	Opportunities to include measures related to ADEs
Physician Compare	<ul style="list-style-type: none"> ▪ Consumer-oriented Web site providing information on physician quality and patient experience ▪ Quality measures including those reported under the Physician Quality Reporting System (PQRS) 	No	No	Opportunities to include measures related to the specific ADE targets

Table D–1. Overview of CMS Programs and Initiatives That Support ADE Prevention (continued)

Program/Initiative	Description	General ADEs Addressed	ADE Targets (Anticoagulants, Diabetes Agents, Opioids) Specifically Addressed?	Opportunities
Related Initiatives Addressing ADEs				
Initiative To Reduce Avoidable Hospitalizations Among Nursing Facility Residents	<ul style="list-style-type: none"> ▪ Interventions to enhance care coordination for long-stay nursing facility residents ▪ Goals: Reduce avoidable hospital transfers or readmissions, improve quality, lower costs, increase patient safety 	<ul style="list-style-type: none"> ▪ Coordinating management of prescription drugs to reduce risk of ADEs 	No	Opportunity to expand focus to include specific drug classes
Related Initiatives Addressing ADEs				
Quality Improvement Organizations	<ul style="list-style-type: none"> ▪ Network of organizations focused on improving quality of care for Medicare beneficiaries 	<ul style="list-style-type: none"> ▪ Patient Safety and Clinical Pharmacy Services Collaborative focuses on improving quality and safety among high-risk patients, increasing medication therapy management, detecting pADEs and ADEs and reporting on ADEs. ▪ Improving Care Transitions and Readmissions focuses on improving effectiveness of pharmacotherapies, increasing patient understanding of medications, detecting ADEs. 	<ul style="list-style-type: none"> ▪ Reporting on <ul style="list-style-type: none"> – The rate of Adverse Drug Events – The potential Adverse Drug Events – Number of beneficiaries on warfarin with International Normalized Ratio (INR) in controlled range – Rate of beneficiaries on warfarin that have INR monitored monthly – Rate of beneficiaries with HbA1c >9% – Rate of beneficiaries prescribed a potentially inappropriate antipsychotic medication 	

Table D–1. Overview of CMS Programs and Initiatives That Support ADE Prevention (continued)

Program/Initiative	Description	General ADEs Addressed	ADE Targets (Anticoagulants, Diabetes Agents, Opioids) Specifically Addressed?	Opportunities
Related Initiatives Addressing ADEs				
Medicare Part D/Opioid Overutilization Policy	<ul style="list-style-type: none"> ▪ Part D sponsors are expected to conduct retrospective drug utilization review and engage in case management for beneficiaries meeting threshold for potential opioid overutilization; Part D sponsors are also expected to employ appropriate controls on coverage of opioids (safety edits, quantity limits). 	<ul style="list-style-type: none"> ▪ Opioid overutilization in Part D 	<ul style="list-style-type: none"> ▪ Partially; Part D beneficiaries meeting threshold for potential opioid use; opioid policy not applicable to other ADEs (anticoagulants and diabetes agents) 	Sponsors may employ MTM to address opioid overutilization.
Regional Chief Medical Officers	<ul style="list-style-type: none"> ▪ Serve as CMS liaison with medical community. 	<ul style="list-style-type: none"> ▪ Provide education on identification and reduction of ADEs. ▪ Participate in intra-agency programs, including Prescription Drug Monitoring Program. ▪ Present on importance of reducing ADEs across region. ▪ Work on appropriate use of antipsychotics in nursing homes. 	<ul style="list-style-type: none"> ▪ Importance of controlled blood pressure and management of diabetes; appropriate use of antipsychotics in nursing home; and medication reconciliation ▪ Educate health care professionals about specific ADE targets on ad hoc basis. 	

Table D–1. Overview of CMS Programs and Initiatives That Support ADE Prevention (continued)

Program/Initiative	Description	General ADEs Addressed	ADE Targets (Anticoagulants, Diabetes Agents, Opioids) Specifically Addressed?	Opportunities
Related Initiatives Addressing ADEs				
National Coverage Determination	<ul style="list-style-type: none"> ▪ Determines coverage policies for Medicare services and equipment 	<ul style="list-style-type: none"> ▪ Two determinations directly relate to prevention of ADEs. 	<ul style="list-style-type: none"> ▪ Medicare coverage for home prothrombin time testing to help patients on warfarin who may be out of therapeutic range ▪ Pharmacogenomic testing to inform physicians of gene variations that might increase or decrease patient’s reaction to warfarin ▪ Coverage for home blood glucose monitoring ▪ Coverage for testing blood glucose levels in pharmacy 	Opportunities to expand coverage determinations to further target reduction in ADEs
State Medicaid Drug Monitoring	<ul style="list-style-type: none"> ▪ State Medicaid agencies use electronic monitoring system to screen prescription drug claims. 	<ul style="list-style-type: none"> ▪ Drug utilization review looks for duplication, contraindications, incorrect dosage or duration. 	<ul style="list-style-type: none"> ▪ Depends on State 	Opportunity to reach out to States to focus on ADEs related to specific drug classes

Abbreviations

ACO	Accountable Care Organization
ADE	adverse drug event
CfC	Condition for Coverage
CHIP	Children’s Health Insurance Program
CMS	Centers for Medicare and Medicaid Services
CPOE	Computerized Provider Order Entry
CoP	Condition of Participation
EHR	electronic health record
HbA1c	Hemoglobin A1c
INR	international normalized ratio
MTM	medication therapy management
pADEs	potential adverse drug events
PCMH	Primary Care Medical Home
PQRS	Physician Quality Reporting System
VTE	venous thromboembolism



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