Suggested citation:
Foreword
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<td>AoA</td>
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<td>ASPE</td>
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<td>Office of the National Coordinator for Health Information Technology</td>
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<td>VA</td>
<td>Department of Veterans Affairs</td>
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## Acronyms

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<td>aPTT</td>
<td>Activated Partial Thromboplastin Time</td>
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<td>Condition of Participation</td>
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<td>Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly</td>
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<td>HbAlc</td>
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<td>HVBP</td>
<td>Hospital Value-Based Purchasing</td>
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<td>Integrating Care for Populations and Communities Aim</td>
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Executive Summary

The National Action Plan for Adverse Drug Event Prevention has two key objectives: identify common, clinically significant, preventable, and measurable adverse drug events (ADEs); and align the efforts of federal health agencies to reduce patient harms from these specific ADEs nationally.

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

The three initial targets of the Action Plan are:

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

The 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 care 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, 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 for high-risk settings where ADE prevention strategies may be lacking (e.g., care transitions, 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 improve 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.

HHS plans to release the final National Action Plan for Adverse Drug Event Prevention, following issuance of this draft Plan and review of public comments. The success of the Action Plan will depend upon ongoing coordination and collaboration across the federal government and among government agencies, national experts, and key public and private stakeholders. The 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 Action Plan. As progress is made toward reductions in ADEs from the initial targets of the Action Plan (i.e., anticoagulants, diabetes agents, opioids), efforts will need to be re-tooled to additional and newly-emerging medication safety targets.
Introduction

This National Action Plan for Adverse Drug Event (ADE) Prevention seeks to engage all stakeholders in a coordinated, aligned, multi-sector, and health literate effort to reduce ADEs that are the most common, clinically significant, preventable, and measurable. The Action Plan identifies the federal government’s highest priority strategies and opportunities for advancement that 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, in conjunction with the Federal Interagency Steering Committee and Workgroups for ADEs, led the development of the Action Plan. Specifically, representatives of up to 13 federal agencies and non-federal subject matter expert consultants contributed to the Action Plan to draw attention to ADEs as a major patient safety and public health issue.

The 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 who can organize and take action towards preventing high-priority ADEs.

The Action Plan is organized into seven sections. The first four sections outline the scope and development of the 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 Action Plan address in detail the high-priority ADE targets (anticoagulants, diabetes agents, and opioids) that are the focus of this Action Plan, highlighting the most pertinent actions to potentially advance the areas of surveillance, evidence-based prevention tools, incentives and oversight, and research (unanswered questions), as well as the role of health information technology (HIT). The final section presents conclusions and outlines next steps.
Adverse Drug Events: Magnitude of the Problem

ADE Prevention is a Patient Safety Priority

Adverse drug events (ADEs) have 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. These harms can include, but are not limited to, medication errors, adverse drug reactions, allergic reactions, and overdoses [1]. In 2006, 82% of the United States (U.S.) population reported using at least one prescription medication, over-the-counter medication, or dietary supplement, and 29% reported using five or more prescription medications [2]. Among older adults (65 years of age or older), 57-59% reported taking five to nine medications and 17-19% reported taking 10 or more [2]. 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 long-term care (LTC) settings (e.g., nursing homes). The likelihood of ADEs occurring may also increase during transitions of care (transitions from one health care setting to another) when information may not be adequately transferred between health care providers [3] or patients may not completely understand how to manage their medications [4, 5, 6].

In inpatient settings, research indicates that ADEs are the single largest contributor to hospital-related complications [7]. ADEs comprise an estimated one-third of all hospital adverse events [8], affect approximately two million hospital stays annually [8, 9], and prolong hospital length of stay by approximately 1.7 to 4.6 days [9, 10, 11]. ADEs have also been identified as the most common causes of post-discharge complications (those occurring within three weeks of hospital discharge), accounting for two-thirds of all post discharge complications – more than half of which are likely preventable [12]. In outpatient settings, nationally representative surveillance data indicate that ADEs account for over 3.5 million physician office visits [13], an estimated one million emergency department (ED) visits [14], and approximately 125,000 hospital admissions each year [14].

ADEs impose a huge financial burden on annual health care expenditures, costing up to $5.6 million per hospital [10, 15]. Depending on the type of ADE, overall ADE costs range from $677 to over $9,000 per
Introduction

National Action Plan for Adverse Drug Event Prevention  |   6

patient [11, 16]. National estimates suggest that ADEs contribute an additional $3.5 billion dollars to U.S. health care costs [17]. 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 [13, 18]. These emergency visits and hospital admissions from largely preventable ADEs contribute to an enormously over-burdened Medicare system [8].

Focus on High-Impact Targets and Populations

The National Action Plan for ADE Prevention seeks to identify common, clinically significant, preventable, and measurable ADEs. There is a key group of ADEs that 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 this Action Plan were identified as three of the most commonly implicated drug classes in ADEs: anticoagulants (bleeding), opioids (delirium/mental status changes), and insulin (hypoglycemia) [8]. 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 [18, 19]. In a recent, nationally-representative sample of hospital admissions for ADEs among older adults (65 years of age or older), an estimated two-thirds of admissions involved just four medication classes, three of which are targets of this Action Plan: anticoagulants (e.g. warfarin), insulin, and oral diabetes agents (e.g., sulfonylurea) [19]. A significant proportion of ADEs in this sample resulted from unintentional overdoses or supratherapeutic effects (e.g., bleeding due to excessive anticoagulation or hypoglycemia from excessive insulin administration) [19].

Most Vulnerable Populations

It is recognized that several patient populations may be especially vulnerable to ADEs (e.g., the very young and older adults, those with low socioeconomic status [SES] or low health literacy, those with limited access to health care services or certain minority races or ethnic groups). To date, data
commonly implicates age as a principle underlying risk factor for ADEs and suggests that older adults, likely owing to altered pharmacokinetics, polypharmacy, or cognitive decline, are particularly vulnerable to ADEs [20, 21, 22]. For example, older adults (65 years of age or older) comprise approximately 35% of all inpatient stays, but contribute to approximately 53% of inpatient stays complicated by ADEs [Figure 1] [9, 16]. In the outpatient setting, national surveillance data indicate that older adults are two to three times more likely to have an ADE requiring physician office or ED visit and seven times more likely to have an ADE requiring hospital admission [Figure 2] [18, 19].

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, which is more than double its projected population of 40.2 million in 2010 [23]. Spending in the U.S. for prescription drugs was $259.1 billion in 2010 and is expected to double over the next decade [24]. Spending on the Medicare Part D program alone is estimated to have reached $60 billion in 2011 [25].

Figure 1. ADEs by Age: Inpatient Settings [9, 16]
Underserved and Rural Communities

Any steps to reduce the incidence of ADEs must 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 [26, 27].

Limited staff resources and slower adoption of EHRs impact 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 towards a more seamless system for reporting these errors through the use of EHRs, underserved communities will be at a disadvantage as adoption rates of EHRs continues to be higher within facilities with more financial resources, and rural communities continue to lag behind their urban counterparts [28, 29].
Implementing 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 [30]. 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 [31]. 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 that serve as a valuable tool to track inappropriate dosages, drug-drug interactions, and drug-allergy interactions.

Even beyond the technology, 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 of technology to access remotely delivered care can result in both direct intervention and enhanced patient education. Provider involvement is crucial to support consumer engagement in shared decision-making regarding medication management. This may be more of a challenge within underserved and rural communities as evidence suggests that individuals in rural communities and those with lower SES have lower health literacy [27].

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, while the majority of CAHs report quality measure information to Hospital Compare, they are exempt from this requirement, which means that changes in Centers for Medicare and Medicaid Services (CMS) programs and policies may not have the same impact on some rural populations.

Lastly, within underserved communities, there is a significant delay in the translation of research into practice [32]. As such, 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 [33]. 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 healthcare-associated infections, ADEs, and other complications of health care delivery through quality and safety promotion efforts;
- Establish the Partnership for Patients, a new public-private partnership that will help improve the quality, safety, and affordability of health care for all Americans.

In December 2011, the U.S. Senate sent a bi-partisan letter to the Secretary of HHS requesting that the Department convene a federal interagency taskforce 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 taskforce include in their considerations: care transitions, the role of HIT, identification of existing and needed measures, and the impact of new Medicare reimbursement models. The 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 [34].
**Structuring the 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 Action Plan would focus on those ADEs that account for the greatest number of measurable harms, currently can be effectively measured, and are considered largely preventable. Among the drug classes that were considered for the Action Plan targets were: anti-infectives, antineoplastic agents, 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 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 that 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 3]. Additionally, each FIW considered Health Information Technology (HIT) as a potential resource which could enhance the work in each of these areas.
The release of the 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 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; patient and consumer representatives; and other private sector stakeholders. Consequently, the Office of Disease Prevention and Health Promotion, 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 Action Plan will provide both updates on progress in addressing the three high-priority ADE targets as well as expansion to other drug classes.
References


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National Action Plan Scope and Development

Scope of the National Action Plan for ADE Prevention

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

The Action Plan is intended to address direct patient harms from prescribed medication use [2]. The Action Plan seeks to identify, collate, and communicate opportunities and gaps within federal systems as well as 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. Additionally, the 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 National Action Plan for ADE Prevention begins with the most fundamental charge to health care systems and providers, “First, do no harm.”

Considering the breadth of the field of harms resulting from medication use, the Federal Interagency Steering Committee decided to narrow the focus of the Action Plan, with the intent of expansion to a wider array of topics and drug classes in the future. As such, the Action Plan does not address circumstances beyond the therapeutic use of medications such as illicit or recreational drug use, drug withdrawal, or using medications in acts of intentional self-harm (e.g., suicide or suicide attempts). Although important public health issues, non-adherence to medication regimens, under-treatment of
diseases, and underutilization of chemo-prophylaxis are also not the focus of the Action Plan. Additionally, the 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 Action Plan, the Steering Committee considered several models for ensuring a comprehensive focus in the effort to reduce ADEs. Leaders of each FIW agreed that the National Strategy for Quality Improvement (National Quality Strategy) incorporated all of the principles and addressed each of the challenges needed 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, 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 Strategy 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 Action Plan. The sixth priority is included
in the section on Incentives and Oversight Opportunities. One of the key principles in the Action Plan is a focus on patient-centered care and patient participation in the delivery of health care. This patient-oriented focus is an essential component to ensure the successful management of chronic conditions that lead to the use of most prescribed medications. The National Quality Strategy 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 Action Plan, the FIWs for ADEs 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 the areas of prevention, surveillance, incentive 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 in order to strengthen existing resources; and
- 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 on enhancing resources in such ways that could support health care systems and providers.

Consequently, the 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 the Steering Committee for the National Action Plan to Prevent Healthcare-Associated Infections established, 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
- **Investigation** – Identify current knowledge gaps and future research needs (unanswered questions) for ADE prevention

Another aspect of the organization of the Action Plan is the contributions of health information technology. At the onset, the ADE Steering Committee recognized the potential for HIT to support all aspects of the Action Plan including measurement, incentives, quality measure development and reporting, and prevention. Examples of how HIT can support the Action Plan are outlined in **Table 1**.

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

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<th>Focus Area</th>
<th>Health IT Feature</th>
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<tbody>
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<td>Surveillance</td>
<td>Electronic data transmission</td>
<td>▪ Real-time data reporting</td>
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<td>▪ Reduced provider burden</td>
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<td>Prevention</td>
<td>Clinical decision support</td>
<td>▪ Flow sheets</td>
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<td>Incentives</td>
<td>Electronic health records</td>
<td>▪ Meaningful Use</td>
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<td>Research</td>
<td>Data repositories</td>
<td>▪ Answer research questions</td>
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<td>▪ Identify best practices</td>
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<td></td>
<td></td>
<td>▪ Develop new research questions</td>
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Furthermore, leveraging HIT helps align the 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”, HIT could help in the identification of effective interventions to prevent ADEs and accelerate integration of ADE monitoring and prevention strategies into the practice of daily medicine. A “Learning Health System” also has the potential to answer additional research questions to help advance the field of medication safety.
References


This section of the Action Plan reviews how 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

Within each section of the Action Plan that addresses the three high-priority ADE targets, ADE surveillance metrics suggested in this section are then matched with existing federal data sources and opportunities for advancing surveillance to drive improvement are further described.

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 are 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 vs. Signal Detection

Public health surveillance can be used to quantify the scope and magnitude of known public health issues (e.g., disease tracking). Public health surveillance can also be conducted to identify new or previously unrecognized health issues (e.g., outbreak detection). In choosing surveillance metrics for the National Action Plan for ADE Prevention, 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 can then be addressed (i.e., for the purposes of signal detection).

Active Surveillance vs. Passive Surveillance (Voluntary Reporting)

Active surveillance involves proactively collecting information on a health condition. Active surveillance traditionally involves collection of 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. While 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 vs. Potential Problems/Medication Errors

Health surveillance can be carried out to identify potential problems or risk factors (e.g., medication errors that can potentially lead to ADEs, potential medication-related problems brought about by polypharmacy, etc.) that may lead to patient injury; 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, is often 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 surveillance of ADEs 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 or ICD-10 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. Diagnostic codes that do incorporate drug attribution of an adverse event to a drug (i.e., Error codes [“E-codes”]) are underutilized and have been found to lack sensitivity for capturing ADEs [4]. Laboratory data may aid in identification of 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.

To address limitations of administrative claims data, review of clinical documentation 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 non-adherence, under-treatment, 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 under-treatment or medication omission is beyond the initial scope of this particular 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 interpretation of ADE incidence or burden by placing these estimates in 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, considerations of 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

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

Setting

Surveillance commonly focuses on a specific setting (e.g., hospitalized patients) and may then expand to other settings (e.g., ambulatory patients, patients in 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 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 gaps for federal partners to optimize ADE surveillance efforts that are addressed in further detail under each of the high-priority drug sections addressed later in the 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
   - 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
   - Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS)

3) Identification of adverse events from administrative claims meta-databases
   - 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

While 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/VA ADERS
The federal passive (voluntary) reporting systems such as FDA’s Adverse Event Reporting System (FAERS) and VHA’s Adverse Drug Event Reporting System (VA ADERS) are constructed to identify (and have identified many) signals of previously unrecognized, underappreciated, or rare ADEs. To do so they are designed to include reports in which the adverse event may or may not be related to the identified drug and are not designed for complete accounting of ADEs or calculating population-based estimates.

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 codes to enumerate the risks of medication-related harms. However, claims data has 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 > 125 million lives, which do 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 now can be extrapolated to provide national estimates and for some specific common ADEs, HCUP may be able to provide regional as well.

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, etc.). CDC’s National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project can provide annual national estimates of ED 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.

VHA’s active surveillance system focuses on quality improvement for a selected population utilizing the VHA’s inpatient and outpatient care settings. The system is comprised of comprehensive Drug Use Evaluation (DUE) program and a Medication Use Evaluation Tool (MUET), which identifies patients at high risk for ADEs based upon pharmacy, laboratory, and diagnostic triggers. The system exemplifies the
importance of making surveillance data available to health care providers in real-time and providing lists of at-risk patients in order to facilitate preventive measures and mitigate risks of potential ADEs in the patient populations at highest risk.

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 4 highlights the strengths and limitations of the federal systems that can be used to conduct ADE surveillance.

**Figure 4. Strengths and Limitations of Federal Systems that Conduct ADE Surveillance [8]**

<table>
<thead>
<tr>
<th><strong>S: Strengths</strong></th>
<th><strong>W: Weaknesses</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inpatient and outpatient settings addressed</td>
<td>• Some critical settings unaddressed (e.g., long-term care facilities, transitions of care)</td>
</tr>
<tr>
<td>• Majority capture ADEs from high-priority drug targets (i.e., anticoagulants, diabetes agents, opioids)</td>
<td>• Highly variable sensitivity, specificity, PPV, and NPV of diagnostic and procedural coding (i.e., ICD-9 and CPT) in capturing ADEs (i.e., not designed or intended for ADE surveillance)</td>
</tr>
<tr>
<td>• Flexibility</td>
<td>• Variable in their ability to link outcomes (harms) of interest to drugs</td>
</tr>
<tr>
<td>• Timeliness</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>O: Opportunities</strong></th>
<th><strong>T: Threats</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Harnessing of large datasets through public-private collaborations (e.g., FDA Sentinel Initiative)</td>
<td>• Funding to support ongoing analyses of surveillance data</td>
</tr>
<tr>
<td>• Leveraging of linked EHRs and new communication technologies</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ADEs = adverse drug events; CPT = Current Procedural Terminology; EHRs = electronic health records; ICD-9 = International Classification of Diseases, Version 9; 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.

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. 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.

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 model 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 [9]. 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 [10, 11] 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. Collaboration on methods of monitoring across federal agencies that directly care for patients at risk for ADEs as well as with non-federal partners could aid the efficacy and efficiency of efforts. This would require an administrative structure to foster such ongoing collaborations and communication in this area.
References


Multiple factors may contribute to ADEs that occur in inpatient, outpatient, and other health care settings (e.g., long term care facilities), 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 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 5**, which identifies the root causes of an event or situation, presents the proximate and latent determinants of ADEs. Although the key determinants presented in the figure 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 5. Fishbone Diagram: Key Determinants of 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 (“polypharmacy”), 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]. Additionally, they 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 that affect the kinetics and dynamics of numerous drugs 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]. Additionally, poor health literacy has been implicated as a contributing factor to ADEs [6].

Provider factors that may contribute to ADEs include those of physicians, pharmacists, or nurses. As indicated in Figure 5, these may include errors involved in medication prescribing, dispensing, or administration [6, 7, 9, 10].

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

Organizations may use this model of key determinants for ADEs to ensure consideration of patient, provider, technical, organizational, and systemic factors to prevent ADEs. Specific organizational changes to address ADEs must follow a careful root cause analysis that identifies targets for intervention. 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 improve the sustainability of the health care system, reduce costs, and improve quality of care for patients. Models that potentially can be leveraged to further target high-priority ADEs include: Patient-centered Medical Homes (PCMH), Accountable Care Organizations (ACO), and Team-based Health Care. Summaries of these models can be found in Appendix C.
References


Incentives and Oversight Opportunities

The U.S. Department of Health & Human Services (HHS), specifically the Centers for Medicare & 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, 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 Conditions of Participation (CoPs), Conditions for Coverage (CfCs)\(^1\), and long-term care facility (LTCF) requirements\(^2\) are the federal health and safety requirements that hospitals and other providers and suppliers must meet to participate in the Medicare and Medicaid programs. The CoPs/CfCs 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 Medicare

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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, but not all, of these ADE-related regulations and guidelines.

**Regulations and Interpretive Guidelines**

**Hospitals**

The hospital CoPs address ADEs in two ways. First, 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 in accordance with accepted standards of practice. 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. Additionally, 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 the requirements for hospitals.

**Long-Term Care (LTC)**

The LTC regulations 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 are free of any significant medication errors. The LTC facility regulations also require that each resident’s drug regimen be free from unnecessary drugs, with a 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 these reports must be acted upon. 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 assuring 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. Since 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 Certification**

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 either the survey agency or the AO and which is appropriately implemented.

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**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**

The Hospital Inpatient Quality Reporting (IQR) Program requires hospitals paid under the Inpatient Prospective Payment System (IPPS) to report on process, structure, outcome, and patients’ perspectives on care, efficiency, and costs of care measures. Performance of quality measures are publicly reported on the CMS Hospital Compare website. In implementing the Hospital IQR program, CMS expects the measures used for public reporting will continue to evolve based on program needs, high-priority areas for quality measures, and other factors. CMS holds the authority to adopt measures addressing ADEs for the Hospital IQR program. Measures implemented in the Hospital IQR program also may be adopted for use in other initiatives linking quality to payment, such as the Hospital Value-Based Purchasing and the Hospital Acquired Condition Reduction programs.

**CMS Demonstration Projects**

The CMS Innovation Center develops and tests new payment and service delivery models. Within this Center, there are at least five programs which address ADEs.

**Health Care Innovation Awards (HCIA)**

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

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1 More information on the Hospital IQR program is available at: [https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/HospitalRHQDAPU.html](https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/HospitalRHQDAPU.html)

**Pioneer Accountable Care Organizations (ACO) Model**

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. Many of the Pioneer ACOs have done work in measuring and reducing ADEs. As an example, one Pioneer ACO has had a long history of measuring and reporting safety events of all types via a safety reporting systems at each site within its network. For measurement, it has focused on system process measures (e.g., implementation of barcoding, computerized order entry, electronic prescribing, and anticoagulation management services). In addition, the Pioneer ACO has been working to standardize medicine decision support (e.g., medication reconciliation, allergy checking, drug interaction checking, duplicate therapy checking, etc.).

**Multi-Payer Advanced Primary Care Practice (MAPCP)**

The Multi-Payer Advanced Primary Care Practice (MAPCP) demonstration includes multi-payer 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 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 HIT 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, and changes to lower cost medication. In addition, providers at practices with advanced electronic

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2 More information on the MAPCP is available at: [http://innovation.cms.gov/initiatives/Multi-Payer-Advanced-Primary-Care-Practice/](http://innovation.cms.gov/initiatives/Multi-Payer-Advanced-Primary-Care-Practice/)
health records (EHRs) receive alerts for patients that need refills in order to keep track of patients’ medications, and to identify duplications and drug-drug interactions.

**Community-based Care Transitions Program**

The goals of the Community-based Care Transitions Program (CCTP) are to improve transitions of beneficiaries from the inpatient hospital setting to other care settings. All of 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.

**Partnership for Patients**

The Partnership for Patients is a public-private partnership working to improve the quality, safety, and affordability of health care for 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 ten 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 and Medicaid Innovation (CMMI), has launched the “Initiative to Reduce Avoidable Hospitalizations among Nursing Facility Residents”. 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.

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i More information on the CCTP is available at: [http://innovation.cms.gov/initiatives/CCTP/](http://innovation.cms.gov/initiatives/CCTP/)


**Hospital Value-Based Purchasing and the Affordable Care Act**

With the 2010 passage of the Affordable Care Act, CMS launched the Hospital Value-Based Purchasing (HVBP) program,¹ which provides powerful incentives, both financial and non-financial, to improve quality of care. CMS is considering whether to propose ADE measures for future updates to the program.

**Medicare and Medicaid Electronic Health Record (EHR) Incentive Programs**

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).² In order to qualify for Meaningful Use incentive payments, each provider category (eligible providers, eligible hospitals, and CAHs) must meet different functional objectives.

Providers must report four measures related to ADEs:

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

In addition, there are specific measures that address the prevention or reduction of ADEs related to the three main drug classes. Additional measures can be developed and electronically specified in the future for a more diverse range of ADE prevention and monitoring.

Given that existing EHR specifications that address high-priority ADE targets were limited, at the request of the HHS Office of the National Coordinator (ONC) for Health IT, the FIWs for ADEs initiated discussions among the federal partners to identify possible requirements that the EHR Meaningful Use 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...

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advance the prevention of ADES are addressed in the drug class-specific Incentives and Oversight sections.

**Physician Quality Reporting System**
The Physician Quality Reporting System (PQRS)<sup>1</sup> provides a series of incentive payments to eligible professionals for meeting satisfactory reporting criteria on quality measures. Those who do not meet the criteria receive negative payment adjustments. In an effort to align with Meaningful Use, PQRS will be introducing two measures that address ADEs for the 2014 Program Year. These measures address:

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

PQRS holds an annual call for measures where stakeholders submit their quality measures for consideration in the program. Through the call for measures and continuing alignment efforts with other quality programs, additional ADE measures could be introduced in the PQRS.

**Physician Feedback Program and Value-Based Payment Modifier**
The Physician Feedback Program/Value-Based Payment Modifier<sup>ii</sup> is a Physician Value-Based Purchasing Program, whose goal is 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 reports to physicians and groups of physicians that measure the amount of resources and quality of care they furnish to Medicare beneficiaries. CMS, beginning in 2015, is also required to apply a separate, budget neutral value-based payment modifier to the Physician Fee Schedule payment formula based upon a physician’s or a physician group’s quality of care compared to cost during a performance period. Quality of care and cost must be evaluated based on the comparison of a composite of quality and a composite of cost measures. CMS has aligned the quality measures in the quality composite of the value based payment

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<sup>ii</sup> More information on the Physician Feedback Program/Value Base Payment Modifier is available at: [http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeedbackProgram/index.html?redirect=/PHYSICIANFEEDBACKPROGRAM](http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeedbackProgram/index.html?redirect=/PHYSICIANFEEDBACKPROGRAM)
modifier with the quality measures within the PQRS Program. These measures may include quality measures related to patient safety and any adverse drug event. CMS anticipates continued enhancements to the composite measures for quality of care and resource use for the value modifier as additional quality and resource use measures become available. This also would apply to any newly developed adverse drug event measures.

**Transparency and Associated Incentives**

Public reporting of Medicare data supports transparency, encourages provider accountability, and provides consumers access to data to help make more informed health care decisions.

**Hospital Compare**

The measures currently reported on Hospital Compare include those that are reported under the Hospital Inpatient and Hospital Outpatient Quality Reporting Programs (Hospital Pay for Reporting) and additional measures that many hospitals voluntarily report. Some of these measures are related to reduction of ADEs.

**Physician Compare**

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 to be posted will be addressed in future rulemaking, and will be selected based on a variety of criteria including consumer interest. Selected measures are subject to consumer testing.

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¹ More information on Hospital Compare is available at: [http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/HospitalCompare.html](http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/HospitalCompare.html)

Related Initiatives Addressing ADEs

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

Quality Improvement Organizations

The Quality Improvement Organization (QIO) Program is a network of organizations staffed with physicians, pharmacists, nurses, technicians, and statisticians that are experts in health care quality. Each QIO is responsible for a U.S. state, territory, or the District of Columbia. The current contract focuses on four aims: Improving Individual Patient Care, Beneficiary and Family-Centered Care, Integrating Care for Populations and Communities, and Improving Health for Population 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

CMS requires QIOs to contribute to the aim of reducing and preventing adverse drug events 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 is a Health Resources and Services Administration (HRSA) and CMS co-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 healthcare delivery systems to reduce adverse drug events. The QIOs also target specific populations of focus including beneficiaries taking diabetes agents, anticoagulants, and antipsychotics.

Several QIOs have developed innovative approaches and developed best practices to reduce adverse drug events (ADEs) across several care settings. One QIO has established a multidisciplinary statewide

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1 An overview of the QIO 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
anticoagulation coalition dedicated to improve 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
improving overall medication therapy management, QIOs are required to track and report on measures.
Measures reported by QIOs include, across time, the overall rate of adverse drug events, the rate of
potential adverse drug events, and specific measures targeted to three areas of focus: anticoagulants,
diabetes agents, and antipsychotic medications.

**Improve Care Transitions and Readmissions**

The Integrating Care for Populations and Communities Aim (ICPCA) 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 over-/under-use. 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 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 the initiative.
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 CMOs emphasize the importance of being a meaningful user of EHRs as a means to reduce ADEs.

**National Coverage Determinations**

CMS provides coverage to expedite the diagnosis of ADEs associated with diabetes agents and anticoagulants. 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 use by health care providers in detecting, mitigating, and preventing ADEs in beneficiaries being treated with either anticoagulants or hypoglycemic agents.

Two national coverage determinations (NCDs) directly relate to detecting and preventing adverse drug events 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 to test 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 adverse drug events 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

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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 ADEs 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**

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 Drug Utilization Review (DUR) Program.

The Medicaid DUR Program\(^1\) 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 provides a review of the existing incentives and oversight opportunities that are the mechanisms to encourage reductions in ADEs. As we move towards improved standardization of measurement for ADEs, opportunities to take advantage of these currently-existing mechanisms may be possible to promote safer medication management.

\(^1\) 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](http://medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Drug-Utilization-Review.html).
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. Current U.S. prevalence estimates of AF are approximately 2.6 million persons and predicted to reach 12 million persons by the year 2050 [1]. The prevention and treatment of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is also a growing, important indication for anticoagulants. It is estimated that over 900,000 incident or recurrent, fatal and non-fatal VTE events occur in the U.S., annually [2]. Total annual direct medical costs and indirect costs (including lost earnings from premature mortality) of VTE are estimated to be $13-$27 billion (USD 2011) [3]. Vitamin K antagonists (VKAs) [warfarin], unfractionated heparin (UFH), low-molecular weight heparins (LMWHs) [e.g., enoxaparin, dalteparin], thrombin inhibitors (e.g., argatroban, dabigatran), and factor Xa inhibitors (e.g., apixaban, fondaparinux, rivaroxaban) are critical for the treatment and prevention of these disorders and various inherited hypercoagulability syndromes [4]. As examples of the extensive use of anticoagulants, over 30 million prescriptions for warfarin are written annually [5]; over two-thirds of Medicare beneficiaries with AF use warfarin [6]; total direct expenditures on warfarin have been estimated to be around $158 million per quarter (USD 2010) [7], and prescriptions of new oral anticoagulants (NOACs), such as dabigatran and rivaroxaban, are increasing [7].

Bleeding is the primary ADE of concern with anticoagulants [5, 8, 9]. As such, 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, the additional factors of diet and pharmacogenetics [10, 11]. Bleeding rates with anticoagulants vary across
the types of anticoagulant agents, dosing strategies, prophylactic vs. therapeutic indications, durations of therapy, and patient populations. For warfarin, bleeding frequency has been estimated to be 15% to 20% per year, with life-threatening or fatal bleeding rates estimated at 1% to 3% per year [12]. Bleeding frequencies while on warfarin are approximately five times those expected without warfarin therapy [13]. Pharmacoeconomic data for anticoagulant-related harms are scarce; however, among older adults (age ≥ 65 years), a population shown to be especially vulnerable to ADEs, including anticoagulants ADEs, the annual cost of treating a hospitalization for warfarin-related bleeding is estimated at hundreds of millions of dollars [9, 14].

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 (HIT) resources (e.g., computerized physician order entry, electronic medication administration records, clinical decision support) [15, 16, 17, 18]. These challenges may result from inpatient providers having to rely on a wide range of anticoagulants with differing pharmacodynamic and pharmacokinetic profiles, the acuity and complexity of the hospitalized patient population, frequent transitions between parenterally- and orally-administered agents (e.g., in preparation for surgery or at time of hospital discharge), unique inpatient dosing considerations (e.g., rapidly-changing renal function, extremes of weight), dietary inconsistency (e.g., changing or reduced dietary intake while hospitalized), and the need for interruption of anticoagulation due to exposure to invasive procedures. Care transitions from one setting to another inside the hospital (e.g., intensive care to step-down unit) and at discharge from the hospital to other settings (e.g., to ambulatory care or long-term care can also pose significant challenges to optimal anticoagulant management [19, 20].

Among non-hospitalized patients (i.e., outpatient settings), requirements for frequent monitoring, dose adjustment, and patient contact can often render management of warfarin (the most commonly-utilized anticoagulant in the outpatient setting [21]) labor-intensive and complex [10, 11]. However, patient interaction with coordinated anticoagulation management services [19, 22] and exposure to anticoagulant education [23] have been correlated with positive outcomes as measured by reductions in thromboembolic and health care costs, and less so, hemorrhagic events [24]. The introduction of NOACs to the market may mitigate some of the health care system burdens associated with outpatient warfarin management and the cost-effectiveness and safety of these agents relative to warfarin and LMWHs is
currently being evaluated [25, 26, 27]. Regardless, outpatient anticoagulation management will likely continue to be heavily-relied upon to manage patient populations for whom NOACs are not prescribed.

Additionally, 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 bleeding/stroke, appropriate dosing/administration instructions, and potential for drug-drug and drug-herbal interactions. Other important areas where coordinated outpatient anticoagulation management may play a role for the NOACs include: identifying appropriate patient candidates for these new agents, transitioning safely among older and newer agents, monitoring patients during interruption of therapy (e.g., peri-procedural period), ensuring accurate age- and/or renal function-dependent dose adjustments, helping to define the use and interpretation of potential laboratory coagulation parameters (e.g., thrombin time, anti-factor Xa), providing patient education (e.g., counseling patients on the importance of adherence owing to 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 [20].

Across health care settings (inpatient, outpatient, long-term care), anticoagulants have been consistently identified as the most common causes of ADEs

Inpatient Settings
In a nationally representative sample of inpatient stays, anticoagulants caused an estimated 10.2% of all drug-related adverse outcomes [28], and in a nationally-representative sample of hospitalized Medicare beneficiaries, anticoagulants comprised one-third of all ADEs identified (12 out of 40 events) [29]. Data from inpatient settings suggest that anticoagulant ADEs most commonly result from medication errors, are highly amenable to prevention, and incur significant costs to the health care system with regard to nursing and pharmacy costs [15, 17, 30, 31].

Outpatient Settings
Based on 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 (ED) visits and hospital admissions [9, 32, 33, 34, 35, 36]. Among older adults (age ≥ 65 years), warfarin was
implicated in an estimated 17.3% of ED visits and 33.3% of emergent hospital admissions for ADEs, annually [9, 36]. An estimated two-thirds of all warfarin-related emergent hospital admissions were due to unintentional overdoses (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 [37, 38].

**Long-Term Care Settings**

Data for anticoagulant-related harms in long-term care settings are more limited than for inpatient and traditional outpatient settings, but suggest that anticoagulant ADEs are common causes of preventable harms in long-term care settings as well [39, 40]. 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, the majority of which may be preventable [41]. In one cohort of long-term care residents of nursing homes, an estimated 29% of warfarin-related ADEs and 57% of serious, life-threatening or fatal warfarin-related ADEs were deemed to be preventable [42]. In this study, the percentages of time in the INR ranges of less than 2, 2 to 3, and more than 3 were 36.5%, 49.6%, and 13.9%, respectively [42]. In a retrospective cohort study within five VA nursing homes, INR monitoring frequency was judged to be adequate. However, INRs were in therapeutic range for only 55% of the person-days, with a greater portion of person-time spent in the subtherapeutic (35%) compared to supratherapeutic range (11%) [43]. Patients with a history of a stroke were less likely to spend ≥ 50% of their time in the therapeutic range; providers may have been more conservative in their dosing due to concerns about falls and an increased risk of bleeding [43]. A similar study in long-term care facilities found that patients spent only half of time in therapeutic range, 36% of the time below the therapeutic range, and 13% of the time above therapeutic range [44].

**Anticoagulation therapy is underutilized in the patient populations for whom it is most beneficial**

It is especially important to note that despite a well-established role for anticoagulation in AF patients at moderate to high stroke risk, as well as the prevention and treatment of VTE, U.S. studies have consistently reported underuse of anticoagulants in these patient populations [45, 46, 47], which can
contribute to higher health care costs associated with strokes and VTE that otherwise would be prevented by effective anticoagulation therapy [48, 49]. Consequently, minimizing the burden of ADEs will be important for optimizing uptake of anticoagulation therapy.

In two studies involving a large commercially-insured patient population, less than one-half of high-risk stroke patients with AF received warfarin and over three-quarters of high-risk VTE patients were considered non-compliant with warfarin therapy [50, 51]. A study conducted in a convenience sample of 21 community-based long-term care facilities in a single state found that only 55% of ideal candidates for warfarin therapy were receiving this therapy [44]. The factors underlying underutilization of anticoagulants have not been explored extensively, but may include provider and patient concerns around supratherapeutic INRs/bleeding risks [52] and lack of patient understanding of the importance of and indications for anticoagulation [53, 54]. Patients from rural or remote regions may be at an increased risk of both under-treatment with anticoagulants and anticoagulant ADEs because of challenges in access to health care providers and 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 [47, 55]. Reluctance on the part of rural providers to prescribe warfarin to patients in rural areas owing to the difficulties in follow-up and monitoring also may contribute to underutilization of anticoagulants in the population [47]. Moving forward, a better understanding of the extent of under-treatment with anticoagulants and the reasons underlying it is needed for rural populations and other patient populations who may be especially vulnerable to ADEs based on race/ethnicity, socioeconomic status, educational attainment, low health literacy, and physical distance from providers.

Although it is not the intent of this Action Plan to directly address underutilization of anticoagulation, it is hoped that targeting collective patient safety efforts at the 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. Future public health initiatives through Federal interagency collaborations and public-private sector partnerships will need to foster a comprehensive approach to optimizing anticoagulation management if health system capacity and provider efforts in this area are to be strengthened.
Surveillance

Optimal use of anticoagulants requires accurate, timely, and adequately-representative information on the “real-world” risks of bleeding complications and other anticoagulant ADEs—at national-, regional-, and facility-levels.

Although clinical trials have well-established the safety profile of various currently-available anticoagulants, these trials often exclude the patient populations at highest risk of ADEs (e.g., older adults, patients with renal insufficiency). Additionally, 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 in order to limit the incidence of ADEs [56]. For these reasons, post-marketing surveillance, like that currently conducted by various federal systems, is crucial for estimating and characterizing the burden of anticoagulant-related harms in clinical practice or “real-world” settings.

Currently-available federal surveillance systems are capable of assessing the national scope of anticoagulant ADE burden and federal systems involved in direct patient care (e.g., IHS, VHA) can capture regional- and facility-level information on the quality of anticoagulant management. Table 2 provides a summary of anticoagulant ADE-related metrics from currently-available Federal surveillance systems.
### Table 2. Summary of Anticoagulant ADE-related Metrics Collected by Currently-Available Federal Surveillance Systems

<table>
<thead>
<tr>
<th>Geographic Scope</th>
<th>Data Collection Methods</th>
<th>Anticoagulation Management or ADE Metrics: Inpatient Settings</th>
<th>Anticoagulation Management or ADE Metrics: Outpatient Settings</th>
</tr>
</thead>
</table>
| National ADE Incidence | Administrative claims and/or EHR data | **AHRQ (NIS):**  
• Inpatient stays with ICD-9 codes 964.2*, E934.2* [28] | **AHRQ (NIS):**  
• Inpatient stays with ICD-9 codes 964.2*, E934.2* [28]  
**FDA (Sentinel Initiative, Mini-Sentinel):**  
• ED visits, hospitalizations for bleeding events and other relevant ADEs (e.g., MI on dabigatran) [57] |
| Medical record review | **AHRQ (MPSMS):**  
• Inpatient stays with combination of laboratory triggers and signs/symptoms in the medical record associated with UFH, LMWHs, or warfarin [37] | **CDC (NEISS-CADES):**  
• ED visits, emergent hospitalizations for laboratory abnormalities, bleeding events, medication errors, other relevant ADEs as diagnosed by clinician and documented in medical record narrative [9, 35] |
| National, Regional-, Facility-level Spontaneous Reports | Voluntary reporting | **DOD (Patient Safety Reporting System):**  
• Any clinician-diagnosed or patient-reported ADEs  
**FDA (FAERS):**  
• Any clinician-diagnosed or patient-reported ADEs  
**VA (VA ADERS):**  
• Any clinician-diagnosed or patient-reported ADEs | **DOD (Patient Safety Reporting System):**  
• Any clinician-diagnosed or patient-reported ADEs  
**FDA (FAERS):**  
• Any clinician-diagnosed or patient-reported ADEs  
**VA (VA ADERS):**  
• Any clinician-diagnosed or patient-reported ADEs |
Table 2. Summary of Anticoagulant ADE-related Metrics Collected by Currently-Available Federal Surveillance Systems (continued)

<table>
<thead>
<tr>
<th>Geographic Scope</th>
<th>Data Collection Methods</th>
<th>Anticoagulation Management or ADE Metrics: Inpatient Settings</th>
<th>Anticoagulation Management or ADE Metrics: Outpatient Settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional, Facility-level ADE Incidence—Quality Improvement</td>
<td>Administrative claims and/or EHR data</td>
<td>VA: Process measures (e.g., out-of-range INR values, Vitamin K orders, transfusions), ADEs (e.g., bleeding events)</td>
<td>DOD (Pharmacovigilance Defense Application System): Outpatient clinic visits, ED visits, hospitalizations using relevant ICD-9 codes and/or CPT codes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VA (VA Integrated Databases): Outpatient clinic visits, ED visits, hospitalizations using relevant ICD-9 codes and/or CPT codes for bleeding events and other relevant ADEs (e.g., MI on dabigatran)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BOP, IHS, VA: Process measures (e.g., TTR, out-of-range INR values, Vitamin K orders, INR monitoring frequency)</td>
</tr>
</tbody>
</table>

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

**In 2015, MSPMS 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, as well as ADEs that are not tied to a specific drug or drug class.

***Currently, FDA Sentinel initiative covers over 125 million lives which do not constitute a nationally representative sample.

**Abbreviations:** ADE = adverse drug event; CPT = Current Procedural Terminology; ED = emergency department; EHR = electronic health record; ICD = International Classification of Diseases; INR = international normalized ratio; LMWH = low molecular weight heparin; MI = myocardial infarction; TTR = Time in Therapeutic Range; UFH = unfractionated heparin

**Future federal strategies will have to address challenges in capturing anticoagulant ADEs based on 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 based on validated diagnostic codes, using consistent definitions of bleeding, ADEs occurring in settings
that have otherwise been poorly studied (e.g., care transitions, nursing homes, home care), and ADEs associated with NOACs (for which well-established process measures are currently lacking). Opportunities to advance anticoagulant ADE surveillance strategies are summarized in Figure 6.

**Figure 6. 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 post-marketing and/or epidemiologic analyses
    - Better distinguish between major and minor anticoagulant-related bleeding events
    - Minimize opportunities for bias or misclassification in characterizing bleeding events based on 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 access to more integrated EHR data with linked pharmacy (medication exposure)-laboratory outcomes data at national and local surveillance levels
  - Improve surveillance of anticoagulant ADEs resulting during care transitions, as well as those occurring in nursing home and home care settings and among vulnerable patient populations such as those residing in rural/remote regions
  - Address challenges in capturing the burden of ADEs among patients who seek care for anticoagulant ADEs outside of integrated healthcare systems
  - Identify appropriate ADE surveillance metrics for NOACs; identify a long-term plan for on-going monitoring of NOAC safety relative to warfarin in “real-world” settings

**Abbreviations:** ADE = adverse drug event; CPT = Current Procedural Terminology; EHR = electronic health record; ICD = International Classification of Diseases; NOACs = new oral anticoagulants; NPV = negative predictive value; PPV = positive predictive value
The most notable opportunities that exist presently are in how and where anticoagulant-related harms are captured. First, ICD-9 codes, including Error (E-) codes, have been commonly relied upon in post-marketing and epidemiologic studies to assess anticoagulant-related bleeding risks \[57, 58, 59\]; however, very few studies have validated the accuracy of diagnostic and procedural codes in identifying the true frequency of anticoagulant-related bleeding events \[60, 61, 62\]. Moreover, the use of E-codes to capture anticoagulation-related bleeding is highly problematic owing to the poor sensitivity of these types of codes for capturing ADEs, including anticoagulant ADEs \[61\]. Second, although definitions of major and minor bleeding in relation to anticoagulants have been universally-agreed upon for some time \[63\], these definitions are not consistently applied across post-marketing and epidemiologic studies, rendering comparisons of study findings as it relates to anticoagulant-related bleeding risks somewhat challenging \[63\]. Third, NOACs present a unique challenge to anticoagulant safety surveillance in that they currently lack well-established process measures (e.g., laboratory coagulation markers) to facilitate adequate monitoring \[20\]. Lastly, few surveillance systems are able to provide robust information regarding anticoagulant ADEs occurring as a result of care transitions issues \[64\] in nursing home or home care settings, and data are currently lacking on underlying causes of anticoagulant ADEs as causes for hospital readmissions.

**Evidence-based Prevention Tools**

Several evidence-based guidelines and prevention strategies/tools targeted at carefully balancing 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. In the inpatient setting, especially, it is acknowledged that there is a subset of especially high-risk anticoagulated patients for whom bleeding cannot be prevented despite optimal care; this is likely less so in the outpatient setting where there remains a need to address the large proportion of anticoagulant ADEs that are considered highly amenable to prevention \[9, 65\]. A summary of existing federal prevention strategies/tools that address safe and effective management of anticoagulation therapy are summarized in **Figure 7**. Several of these strategies/tools are general patient safety or medication safety approaches, but have the potential for
the purposes of health system- and provider-level prevention of anticoagulant ADEs and provision of optimal anticoagulation management.

**Inpatient Settings**

Recognizing that anticoagulants are more likely than other medications to cause harm to patients in inpatient settings due to such factors as complex dosing, requirements for frequent monitoring, transitions between parenterally- and orally-administered agents (e.g., in preparation for surgery or at time of hospital discharge), the most recent (2013) National Patient Safety Goals (NPSG) identified by The Joint Commission (TJC) include NPSG.03.05.01: “Reduce the likelihood of patient harm associated with the use of anticoagulant therapy”. Related goals include, NPSG.03.04.01, “Label all medications, medication containers, and other solutions on and off the sterile field in perioperative and other procedural settings” and NPSG.03.06.01, “Maintain and communicate accurate patient medication information”. Performance elements associated with these goals may include the use of approved protocols for the initiation and maintenance of anticoagulant therapy, use of programmable pumps for UFH therapy, policies that address baseline and ongoing laboratory monitoring for anticoagulants, and education regarding anticoagulant therapy for prescribers, staff, patients, and families [66].

The Institute for Safe Medication Practices (ISMP) “Pathways for Medication Safety” describes a comprehensive set of tools to help hospitals adopt a “process driven, systems-based” approach to reduce medication errors and improve patient care [67]. Systematic processes to ensure inpatient anticoagulation safety can encompass such strategies as use of standardized anticoagulation dosing protocols, implementation of technology (i.e., 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 [19]. The National Quality Forum (NQF), which works to identify and achieve consensus on national health care priorities and goals, has also endorsed a national goal for reducing anticoagulant-related harms by way of Safe Practice #29 (Anticoagulation Therapy): “Organizations should implement practices to prevent patient harm due to anticoagulant therapy” [68].

Goals such as those set by TJC, NQF Safe Practice #29, and ISMP for ensuring the safe use of anticoagulants in inpatient settings suggest that multidisciplinary, coordinated, and systematic
processes will be critical in facilitating reductions in anticoagulant ADEs among hospitalized patients [19, 66, 67, 68], and will be needed to meet the extant challenges inherent to inpatient anticoagulation management. Such challenges may include:

- Acuity and complexity of patient population and the need for more individualized treatments (relative to outpatient settings),
- Lack of nationally-recognized, widely-shared, comprehensive set of best practices or standards focusing specifically on safe use of anticoagulants in hospitalized patient populations, and
- Reliance on highly-multi-faceted interventions for 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 in inpatient settings not as amenable to capture as in outpatient settings).

Opportunities for advancing anticoagulant ADE prevention strategies/tools in inpatient settings, as identified by the NQS Priorities, are summarized in Figure 8 and discussed further below.

Figure 7. Current and Potential Federal Assets Related to Safe Management of Anticoagulation Therapy as Identified by the National Quality Strategy Priorities

<table>
<thead>
<tr>
<th>Resources for Safer Care – Health Care Provider Knowledge</th>
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<tbody>
<tr>
<td>BOP:</td>
</tr>
<tr>
<td>– 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</td>
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<tr>
<td>IHS:</td>
</tr>
<tr>
<td>– National Anticoagulation Training Program—three day certificate training program providing specialized training in anticoagulation and disease management; other federal partners represented (BOP, DOD, VA)</td>
</tr>
<tr>
<td>VA:</td>
</tr>
<tr>
<td>– Education 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, self-learning modules, live broadcasts on anticoagulation management, and C.E. programs on anticoagulation safety</td>
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<tr>
<th>Resources for Patient and Family Engagement</th>
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<tbody>
<tr>
<td>ACL:</td>
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<tr>
<td>– Stanford Chronic Disease Self-Management Education Program—six-week program to help participants better manage their medications, including specific information about anticoagulants</td>
</tr>
<tr>
<td>AHRQ:</td>
</tr>
<tr>
<td>FDA:</td>
</tr>
<tr>
<td>– Medication Guides (available for apixaban, dabigatran, rivaroxaban, and warfarin)</td>
</tr>
</tbody>
</table>
Figure 7. Current and Potential Federal Assets Related to Safe Management of Anticoagulation Therapy as Identified by the National Quality Strategy Priorities (continued)

<table>
<thead>
<tr>
<th>Resources for Communication and Coordination of Care</th>
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<tbody>
<tr>
<td>▪ AHRQ:</td>
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<tr>
<td>– 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)</td>
</tr>
<tr>
<td>▪ BOP, IHS:</td>
</tr>
<tr>
<td>– Anticoagulation Management Electronic Flow Sheet—integrates laboratory and pharmacy data in one location, in an easily accessible format, and in as near real time as possible</td>
</tr>
<tr>
<td>▪ VA:</td>
</tr>
<tr>
<td>– Traveling Veterans Directory—addresses challenges associated with care coordination for Veterans seeking care at a different VA medical facilities when traveling</td>
</tr>
<tr>
<td>– 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 follow up list, calculates TTR, and develops complications reports</td>
</tr>
<tr>
<td>– Electronic consults and templates—coordinates care with outpatient anticoagulation clinics upon discharge</td>
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<tr>
<th>Resources for Science-driven Prevention and Treatment</th>
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</thead>
<tbody>
<tr>
<td>▪ BOP, DOD, IHS, VA:</td>
</tr>
<tr>
<td>– Systematic and coordinated anticoagulation management models of care (i.e., anticoagulation clinics, PST/PSM)</td>
</tr>
<tr>
<td>▪ VA:</td>
</tr>
<tr>
<td>– Medication Use Evaluation Tracker (MUET)—available for dabigatran and rivaroxaban to identify and intervene upon inappropriate use and prevent potential ADEs</td>
</tr>
<tr>
<td>– Electronic decision support templates—for ordering and monitoring NOACs</td>
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<tr>
<th>Resources to Promote Best Practices within Communities</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ VA:</td>
</tr>
<tr>
<td>– Sharepoint Resource Center—lists strong clinical practices, tools, and patient education materials related to anticoagulation management</td>
</tr>
</tbody>
</table>

Abbreviations: ADE = adverse drug event; CE = continuing education; EHR = electronic health record; INR = International Normalized Ratio; NOACs = new oral anticoagulants; PSM = patient self-monitoring; PST = self-testing; TTR = time in therapeutic range

Federal agencies that develop, promote, and incentivize EHR standards play an important role in advancing HIT-based strategies for 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, deliver optimized inpatient anticoagulation management [19], and thus reduce the likelihood of anticoagulant ADEs. Processes and tools for inpatient anticoagulation management should be electronically integrated with the remainder of the health record 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 to promote review of key laboratory values prior to ordering or dispensing anticoagulants will be important. Such strategies could entail 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.

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

Currently, evidence-based guidelines/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 non-profit, multi-disciplinary organization whose goal is to improve quality of care among patients taking antithrombotic medications), are leading the way in fostering sharing and communication of best practices and prevention strategies/tools across health care systems/facilities [69]. However, there remains tremendous opportunity to learn about high-quality facility strategies/tools from the sites of 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 for both VA and Non-VA facilities is summarized in **Table 3**.

**Table 3. Department of Veterans Affairs—National Center for Patient Safety “Actions From VA and Non-VA Facilities To Control Vulnerability” from Anticoagulation**

<table>
<thead>
<tr>
<th>System</th>
<th>Action</th>
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</table>
| Storage | ▪ Limit the availability of anticoagulant drugs from floor stock to reduce misadministration  
▪ Limit the availability of reversal agent drugs from floor stock to reduce misadministration |
| Ordering| ▪ Establish weight-based heparin protocols (to improve consistency) with education on exclusion and inclusion criteria. Close monitoring for success and failures and adjustment of protocol as necessary is commonly seen |
| Preparation | ▪ 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 over infusions occur (250 ml versus 500 ml)  
▪ Provide heparin in dosage forms that are as close as possible to what is ordered (e.g. 5000 U) |
| Distribution | ▪ Use manufacturer’s pre-made solutions to reduce compounding and labeling errors |
Table 3. Department of Veterans Affairs—National Center for Patient Safety “Actions From VA and Non-VA Facilities To Control Vulnerability” from Anticoagulation (continued)

<table>
<thead>
<tr>
<th>System</th>
<th>Action</th>
</tr>
</thead>
</table>
| Administration         | ▪ Establish a food and drug interaction program/policy which 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 | ▪ Establish a pharmacy-based inpatient anticoagulation service to improve monitoring, follow up and transitioning to warfarin  \  
                        | ▪ Standardize the monitoring of anticoagulant laboratory work so that clinical changes are detected early (e.g., hemoglobin, platelets, etc.) |


*It will be important for Federal agencies to play a role in supporting the wide dissemination and uptake of evidence-based strategies for anticoagulant ADE prevention across health care systems and facilities*

The CMS Center for Medicare & Medicaid Innovation-led Partnership for Patients Initiative serves as an example of how federal funding could enhance private sector efforts to prevent anticoagulant ADEs. The goals for Partnership for Patients 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, this initiative has supported large networks of health systems and hospitals (“hospital engagement networks” [HENS]) across 23 states by providing strategies targeted at monitoring safe use of warfarin in inpatient settings [70, 71]. Example metrics these HENs use 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 education
- Percent of patients on warfarin that have dose management protocols
- Percent of patients on heparin dosing protocol
- Percent 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 over 650 hospitals that are part of the HENs with at least 6 months of trend data related to inpatient warfarin safety.

**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 HIT-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-/pharmacist-managed inpatient anticoagulation services and “multi-disciplinary anticoagulation rounds” that include representatives from medicine, pharmacy, and nursing [72, 73, 74, 75]. Additionally, promoting the concept of “anticoagulation stewardship” may go a long way in promoting a “culture of safety” specifically around anticoagulants. Anticoagulation stewardship encompasses a multi-disciplinary, coordinated, and systematic approach to reducing anticoagulant ADE burden. This is analogous to the concept that has been successfully developed to improve the quality of anti-infective utilization in inpatient settings [76]. This concept is also applied around other types of in-hospital complications and adverse events, such as health care-associated infections [77, 78, 79].

A summary of opportunities for advancing anticoagulant ADE prevention strategies/tools in inpatient settings, as Identified by the NQS Priorities, are summarized in Figure 8.

**Figure 8. Opportunities for Advancing Anticoagulant ADE Prevention Strategies/Tools as Identified by the National Quality Strategy Priorities—Inpatient Settings**

- **Safer Care**
  - Wider dissemination of/increase accessibility to evidence-based strategies/tools that address high quality inpatient anticoagulation management
  - Address gaps in evidence and provider knowledge with regard to management of NOACs thru:
    - Development of guidelines/algorithms for safe use and accurate laboratory testing of NOACs
Figure 8. Opportunities for Advancing Anticoagulant ADE Prevention Strategies/Tools as Identified by the National Quality Strategy Priorities—Inpatient Settings (continued)

**Effective Communication and Coordination of Care**
- Improve EHR tools to enable provider access to real-time, integrated, linked pharmacy-laboratory data to facilitate seamless access to pertinent medication and laboratory data and provision of optimal inpatient anticoagulation management, such as:
  - Electronic flowsheets that display trends in daily labs, concomitant medications, reversal medications, etc. that are specific to anticoagulation management
  - Clinical decision support tool specific to anticoagulation management
- Better integrate anticoagulation-specific targets into currently existing care transition models

**Science-driven Prevention and Treatment**
- Promote a multi-disciplinary, coordinated, and systematic approach to inpatient anticoagulation management, e.g.,
  - “Anticoagulation rounds”, pharmacist-/nurse-managed anticoagulation services, “Anticoagulation Stewardship”, “culture of safety” around anticoagulation management
- Better address safe use of anticoagulants commonly utilized in inpatient settings (e.g., argatroban) and NOACs in national health care quality/patient safety measures and in national clinical guidelines

**Promote 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 targeted at anticoagulant ADE prevention among health care systems/facilities

Abbreviations: ADE = adverse drug event; EHR = electronic health records; NOACs = new oral anticoagulants

**Outpatient Settings**
Although prescribing of NOACs is increasing, the most recent data available (2011) suggest that warfarin remains the most commonly-utilized oral anticoagulant in outpatient settings [7, 21]. Well-established, 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, follow-up, 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 where 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, and
- Centralized management of a population of patients with direction provided by different primary or referring physicians for individual patients [80].

_Federal agencies that provide direct patient care should continue to lead the path in exploring ways to further improve uptake of evidence-based, systematic, and coordinated models of oral anticoagulation management associated with reductions in anticoagulant ADEs and health care costs_

In outpatient hospital departments and in the community, anticoagulation clinics (or “Coumadin clinics”) most often deliver systematic and coordinated oral anticoagulation management. In the U.S., it is estimated that there are approximately 3000 such anticoagulation clinics [81]. The VA has long-embraced the model of anticoagulation clinic services. In an internal survey conducted in 2008, more than 95% of VA medical facilities were identified as having specialized outpatient anticoagulation management (including, clinics) [82].

There is a large and long-standing body of evidence that anticoagulation clinic services are associated with improved anticoagulation management. Impact of anticoagulation clinic services on process measures such as higher TTRs, proportion of INR values within target ranges, and reductions in ED visits and hospital admissions for thromboembolic and hemorrhagic outcomes (including major and fatal bleeding episodes) relative to “usual medical care” have been extensively described [24, 83, 84]. In conjunction with quality improvement, anticoagulation clinics have demonstrated reductions in health care costs by $800 to $1600 per patient-per year [80, 85]. Research results suggest that health systems could invest considerable resources to meet this challenge and still save money [86]. Despite this
evidence, it is estimated that only 30–40% of U.S. patients receiving oral anticoagulation therapy are enrolled in such clinics [81]. 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, etc.), and economic factors (e.g., lack of payment/coverage incentives to operate such 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 IHS coordinates (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 to a range of facilities. 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, also could be considered. Potential opportunities for overcoming economic barriers related to wider uptake of anticoagulation clinic services are discussed further below under Incentives and Oversight.

Establishing an anticoagulation clinic is only the first step towards reducing anticoagulation ADEs. Larger remaining challenges include ensuring patients are referred to or utilize such clinics, and optimizing communication among providers caring for the same patient within and outside the clinic. This can be especially true for patients who do not regularly seek care in highly-integrated health care systems and for rural/remote populations.

Although anticoagulation clinic services have proven to be effective means of optimizing anticoagulation management, there are challenges surrounding their use. One is the fact the there will always remain a subset of patients who are at especially high-risk of bleeding despite the use of systematic and coordinated models of anticoagulation care. Second, some patients may simply not be appropriate candidates for such services (e.g., due to their residing in rural/remote areas or a poor history of compliance with scheduled visits). Third, with respect to anticoagulant ADE prevention, anticoagulation clinic services are actually likely to be more impactful from an effectiveness standpoint (prevention of thromboembolic events) [24, 87], than a safety standpoint (prevention of hemorrhagic events) [83, 84].
even though, studies have demonstrated positive, substantial impacts on all fronts—effectiveness, safety, and costs.

Due the factors above, alternative models of oral anticoagulation management that are not dependent on the anticoagulation clinic model have been explored and are currently utilized [88, 89, 90]. The most prominent among them include patient self-testing (PST) and patient self-management (PSM). These are defined as INR testing to be performed by patients in their homes with a drop of blood from the finger (PST) and INR self-testing with patient adjustment of their anticoagulant dose (PSM) [4]. 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 need to facilitate better identification of patients who are appropriate candidates for PST/PSM models of care and improve uptake of such models of care for those patients [69]. For patients residing in rural/remote areas, increasing access to pharmacist services and telephonic management are strategies that could be considered to assist general practitioners in the management of their anticoagulated patients [84, 89, 90].

Although the introduction of the 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 likely 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., peri-procedural period), ensuring accurate age- and/or renal function-dependent dose adjustments, helping to define the use and interpretation of potential laboratory coagulation parameters (e.g., thrombin time, anti-factor Xa), providing patient education (e.g., counseling patients on the importance of adherence owing to 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 [20].

Additionally, 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 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 where such tools could be targeted are discussed below under 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 9.
Figure 9. Opportunities for Advancing Anticoagulant ADE Prevention Strategies/Tools as Identified by the National Quality Strategy Priorities—Outpatient Settings

| Safer Care | ▪ Improve uptake of evidence-based anticoagulation management models, including anticoagulation clinic services and PST/PSM
▪ Address provider concerns around supratherapeutic INRs and resultant under-treatment
▪ Address gaps in evidence and provider knowledge with regard to management of NOACs thru:
  – Development of guidelines/algorithms for safe use and accurate laboratory testing of NOACs |
<table>
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<tr>
<td>Patient and Family Engagement</td>
<td>▪ Improve incorporation of anticoagulation-specific patient management into Chronic Disease Self-Management Education Programs and other patient education/health literacy tools</td>
</tr>
<tr>
<td>Effective Communication and Coordination of Care</td>
<td>▪ Better integrate anticoagulation-specific targets into currently existing care transition models</td>
</tr>
</tbody>
</table>
| Science-driven Prevention and Treatment | ▪ Address factors that contribute to inter-facility variability in anticoagulation services (incl., outpatient clinic services)
▪ Conduct “anticoagulation rounds”, pharmacist-/nurse-managed anticoagulation services, “Anticoagulation Stewardship”
▪ Better address safe use of NOACs in national health care quality/patient safety measures and national clinical guidelines |
| Promote 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 targeted at anticoagulant ADE prevention among health care systems/facilities |

**Abbreviations:** INR = International Normalized Ratio; NOACs = new oral anticoagulants; PSM = patient self-management; PST = patient self-testing
Federal agencies should explore ways to incorporate anticoagulation-specific targets in ADE prevention strategies in long-term care and care transitions settings

Long-term Care Settings

More needs to be learned about the quality and outcomes associated with anticoagulation therapy in long-term care settings, including the extent of adoption and application of best practices for anticoagulant ADE prevention [91]. Barriers to providing high-quality anticoagulation management in long-term care settings have not been thoroughly studied; however, in nursing homes, these may include provider concerns around supratherapeutic INRs and resultant under-treatment of patients, 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, nursing homes especially, 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 long-term care settings. Limited accessibility of EHRs outside a particular facility and the challenge of transmitting pertinent anticoagulation-related data elements, in an efficient manner, to a remote provider who can manage patients’ anticoagulation may complicate anticoagulation services in long-term care settings. Strategies aimed at improving anticoagulation safety and providing high-quality anticoagulation management in long-term care settings may include:

• Standardizing anticoagulation management treatment approaches across long-term care settings, which might 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 [91], or developing long-term care-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 targeted at 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 pre-printed medication orders which identify patient specific goals/target INR ranges), and
• 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, in-home laboratory services are accompanied by reimbursement challenges leading to insufficient monitoring of post-acute patients discharged to home care settings. Changes in reimbursement policy for the use of portable INR devices in the home care setting may allow for more frequent laboratory monitoring to prevent possible complications from anticoagulation therapy in these settings. Alternatively, adequate staff training for 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 facilitate provider access to real-time, linked pharmacy-laboratory data. Lastly, 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 care transitions issues into, within, and out of the hospital that are specific to anticoagulation management [64]. Anticoagulated patients will likely remain at high risk for ADEs as long as there remain sub-optimal 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 networks, 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 follow-up within five days of hospital discharge [75].

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 tenant of ensuring safe care transitions [64], and plays an important role in preventing anticoagulant ADEs. Patient education about warfarin therapy has been associated with stability of therapy as measured by TTR [92] and reductions in hemorrhagic and thromboembolic events [93, 94]. Similarly, reductions in hospital readmission rates have been demonstrated among patients who received education around therapy with LMWHs and fondaparinux relative to patients who did not receive anticoagulant education [95]. However, patient education in and of itself will not likely be sufficient to mitigate the public health burden of anticoagulant ADEs at a population-based level [96]. For example, one study found that current warfarin patient information sheets that are 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 [97, 98].

Another core tenet of care transition models, is medication reconciliation [64], commonly defined as reviewing the 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 [99]. Medication reconciliation as a care transitions 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 ED visits or hospital readmissions for ADEs) remains to be seen [100, 101, 102, 103]. It remains unclear whether this is because medication reconciliation historically
has not been targeted at the highest-risk drugs or patients or because it is probably insufficient in and of itself without additional post-discharge monitoring and care coordination (e.g., clinic-based support, home visits) [64, 101, 102]. Future studies are needed to assess the impact of medication reconciliation, especially when bundled with other care transitions strategies, on the prevention of anticoagulant ADEs.

**Incentives and Oversight**

From the perspective of HHS, incentive and oversight levers potentially can be applied to advance anticoagulant ADE prevention in several categories. These opportunities to advance the prevention of anticoagulant ADEs through incentives and oversight-based strategies are summarized in Figure 10. Some of the levers or programs include CMS reimbursement or coverage of services (e.g., National Coverage Determinations), incentive programs (e.g., EHR Incentive Program), and certification and compliance programs (e.g., Conditions of Participation for critical access hospitals, Five-Star Quality Rating System for nursing homes). Some of these programs are described in more detail in the general Incentives & Oversight Opportunities section of the Action Plan. Policy levers may also reside in other federally-endorsed patient safety and quality measure areas, such as AHRQ’s Patient Safety Indicators (PSIs) and Prevention Quality Indicators (PQIs) [104]. PSIs are a set of indicators that provide information on potential in hospital complications and adverse events following surgeries, procedures, and childbirth; and PQIs are a set of measures that that can be used with hospital inpatient discharge data to identify quality of care for “ambulatory care sensitive conditions” [104]. Future policy efforts targeted at mitigating the burden of anticoagulant ADEs may include an exploration of whether complications of anticoagulation therapy could be considered for incorporation into such measures.
Figure 10. Federal Interagency Workgroup Recommendations for Actions that Can Potentially Advance Policy Strategies for Anticoagulant ADE Prevention

**Actions that Can Potentially Advance Health Policy Strategies for Preventing Anticoagulant ADEs**

**Inpatient Settings**
- Expand national health care quality reporting measures to include concepts related to multi-disciplinary, 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 ADE prevention
- Address payment/coverage barriers to uptake of evidence-based, high-quality ADE prevention strategies (e.g., anticoagulation clinics, 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

**Few nationally-recognized measures that are specific to anticoagulation safety are currently available**

To date, very few measures that are specific to anticoagulation safety have been endorsed by public and private sector organizations (Table 4). This is important because these types of measures are often considered as candidate clinical quality measures in CMS value-based purchasing incentive programs and other types of strategies for improving the quality of care for Medicare beneficiaries, and are often also adopted by facilities in health system quality improvement efforts.
### Table 4. National Quality Foundation (NQF)-Endorsed Health Care Quality Measures Specific to Anticoagulation Safety*

<table>
<thead>
<tr>
<th>Measure ID</th>
<th>Measure</th>
<th>Measure Description</th>
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<tbody>
<tr>
<td>NQF 0374</td>
<td>VTE Patients Receiving UFH with Dosages/Platelet Count Monitoring by Protocol (or Nomogram)</td>
<td>This measure assesses the number of patients diagnosed with confirmed VTE who received intravenous (IV) UFH therapy dosages AND had their platelet counts monitored using defined parameters such as a nomogram or protocol</td>
<td>The Joint Commission</td>
</tr>
<tr>
<td>NQF 0375</td>
<td>VTE Discharge Instructions</td>
<td>This measure assesses the 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, follow-up monitoring, and information about the potential for adverse drug reactions/interactions</td>
<td>The Joint Commission</td>
</tr>
<tr>
<td>NQF 0555</td>
<td>Lack of Monthly INR Monitoring for Individuals on Warfarin</td>
<td>Average percentage of monthly intervals in which individuals with claims for warfarin do not receive an INR test during the measurement period</td>
<td>CMS</td>
</tr>
<tr>
<td>NQF 0556</td>
<td>INR for Individuals Taking Warfarin and Interacting Anti-Infective Medications</td>
<td>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</td>
<td>CMS</td>
</tr>
<tr>
<td>NQF 0586</td>
<td>Warfarin_PT/ INR Test</td>
<td>This measure identifies the 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</td>
<td>Resolution Health, Inc.</td>
</tr>
<tr>
<td>NQF 0612</td>
<td>The percentage of patients taking warfarin who had PT/INR monitoring</td>
<td>The percentage of patients taking warfarin who had PT/INR monitoring</td>
<td>ActiveHealth Management</td>
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*Note: Measures summarized here 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 addressed here.

**Abbreviations:** INR = International Normalized Ratio; PT = prothrombin time; UFH = unfractionated heparin; VTE = venous thromboembolism
Federal partners should better address economic barriers to uptake of evidence-based anticoagulation ADE prevention strategies (e.g., anticoagulation clinic services, PST/PSM)

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

With regard to the first barrier—limits on direct payment to non-physician providers (i.e., pharmacists)—under Medicare Part B, pharmacists currently are considered as “non-advanced practice staff” whose services are charged on the physician’s bill for “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 [105, 106]. 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”, five minutes of time is spent performing/supervising such services, and does not require the presence of a physician. This code can be limiting in that, despite a comprehensive patient evaluation 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 or new medical co-morbidities or dietary change [105, 106]. 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. Nonetheless, this specific barrier is beyond the scope of the 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 2013 top strategic priorities [107]. Other groups are also actively working to advance the recognition of pharmacists as health care providers [108].
With regard to the second barrier—limits on physician billing—the primary issue here relates to the high overhead costs of maintaining anticoagulation clinic services. The 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 ED visits or hospitalizations) from initiating and maintaining coordinated anticoagulation clinic services. 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, etc.) are not directly reimbursable (providers are limited to seeking reimbursement for PT/INR tests performed).

Moving forward, evaluation of the aforementioned economic barriers will be important in advancing evidence-based ADE prevention strategies for both warfarin and the NOACs.

**Health Information Technology (HIT)**

The FIW for Anticoagulant ADEs has proposed EHR (Stage 3) Meaningful Use requirements that can potentially advance anticoagulant ADE prevention

During development of the 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 Action Plan, the FIW for Anticoagulant ADEs discussed and identified various health care quality measures specific to anticoagulant safety that were amenable for incorporation into the EHR-based quality measure strategies. The FIW recommended these measures, presented in Table 5, to the HHS for Health Information Technology (ONC) for consideration as possible candidate measures for Stage 3 EHR Meaningful Use (MU) requirements that potentially can support anticoagulant ADE prevention and monitoring. In making these recommendations, the FIW for Anticoagulant ADEs chose to recommend metrics that were already-existing, nationally-endorsed, and thus, had previously undergone a critical review process, or metrics that closely mirrored recommendations integrated into nationally-recognized clinical guidelines for anticoagulation management.
Table 5. EHR (Stage 3) Meaningful Use Requirements that Can Potentially Advance Anticoagulant ADE Prevention as Proposed by the Federal Interagency Workgroup (FIW) for ADEs

<table>
<thead>
<tr>
<th>Metric</th>
<th>Description and Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Quality Measure Concepts—Eligible Providers</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Percent of patients on anticoagulants with INR test 7 to 14 days following out-of-range INR | Assesses number of patients
  ▪ With non-valvular AF
  ▪ On chronic warfarin therapy for at least 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**
  ▪ Anticoagulation control, as measured by TTR, is improved by prompt, repeat testing after out-of-range INR values [109, 110]
  ▪ NQF Measure 0555
  ▪ 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]
| **Clinical Decision Support (CDS) Rule Concepts—Eligible Providers** | |
| INR Re-testing Evaluation | Clinical reminder to assess need for INR test in patients on chronic warfarin therapy (>180 days) and >30 days since last INR test
  
  **Rationale**
  ▪ NQF Measure 0555
  ▪ 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]
| INR testing—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 re-test.
  
  **Rationale**
  ▪ NQF Measure 0556
  ▪ 2012 ACCP (Chest) Guidelines—Recommendation 3.8: for patients taking VKAs...avoid concomitant treatment with...certain antibiotics (Grade 2C) [4]
**Table 5. EHR (Stage 3) Meaningful Use Requirements that Can Potentially Advance Anticoagulant ADE Prevention as Proposed by the Federal Interagency Workgroup (FIW) for ADEs (continued)**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Description and Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient List Recommendation—Eligible Providers</td>
<td>Patient lists stratified by INR testing interval/time since last INR test (30 days, 60 days, 90 days, &gt;90 days)</td>
</tr>
<tr>
<td>Last INR Test</td>
<td>Rationale</td>
</tr>
<tr>
<td></td>
<td>▪ NQF Measure 0555</td>
</tr>
<tr>
<td></td>
<td>▪ 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]</td>
</tr>
<tr>
<td>EHR Functionality/Usability Recommendation—Eligible Hospitals</td>
<td>It is recommended that EHRs have the capacity to display linked pharmacy and laboratory data pertinent to anticoagulation management. Ideally, an Inpatient Electronic Anticoagulation Management Flowsheet would display necessary data elements:</td>
</tr>
<tr>
<td></td>
<td>▪ In one location,</td>
</tr>
<tr>
<td></td>
<td>▪ In an easily accessible format, and</td>
</tr>
<tr>
<td></td>
<td>▪ As near real-time as possible.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACCP = American College of Chest Physicians; AF = atrial fibrillation; INR = international normalized ratio; NQF = National Quality Forum; TTR = time in therapeutic range; VKAs = vitamin K antagonists (i.e., warfarin)

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**Federal partners should continue to explore health care quality measures that are targeted at optimizing anticoagulation management**

The FIW for Anticoagulant ADEs considered additional metrics in its discussions and articulated areas where there are current gaps in national healthcare quality measures or EHR requirements as it pertains to anticoagulation safety (Table 6). 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, for example, e-prescribing and clinical decisions support tools) likely presents the most efficient and forward approach to measurement and one that minimizes burden of measure reporting by health systems and providers. The potential metrics that require further development and evaluation 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,

• Follow-up on individual time in therapeutic range (iTTR) <65% 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 anticoagulants other than LMWHs/UFH (e.g., argatroban, bivalirudin),

• Metrics targeted at clinical outcomes (e.g., bleeding events) versus limited to process measures, and

• Metrics targeted at transitions of care-based measures (e.g., hospital follow-up with ambulatory care providers upon discharge).

Table 6. Possible Future Areas for New Measure Concept Development Related to Anticoagulant ADE Prevention and Current Barriers to Development

<table>
<thead>
<tr>
<th>Measure Concept</th>
<th>Current Barriers to Development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NOACs</strong></td>
<td>Evolving and early science</td>
</tr>
<tr>
<td>▪ Dosing, adherence, and transitions among older and newer agents</td>
<td>Lack of consensus and/or uniformity across sites as to what constitutes optimal process measures (e.g., inter-facility variations in target aPTTs)</td>
</tr>
<tr>
<td><strong>Parenterally-administered</strong></td>
<td>Quality of diagnostic and procedural coding for capturing anticoagulant-related bleeding events poorly explored to date</td>
</tr>
<tr>
<td><strong>anticoagulants (i.e., hospital uses of anticoagulants)</strong></td>
<td>Associated with complex, difficult-to-measure process metrics (e.g., hand-off’s, communication between inpatient and outpatient providers)</td>
</tr>
<tr>
<td>▪ Pertinent laboratory monitoring parameters</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes-based metrics</strong></td>
<td></td>
</tr>
<tr>
<td>▪ Bleeding events</td>
<td></td>
</tr>
<tr>
<td><strong>Care transitions</strong>-related metrics</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ADE = adverse drug event; aPTT = activated partial thromboplastin time; NOACs = new oral anticoagulants
Research (Unanswered Questions)

As anticoagulation management practices evolve and new anticoagulant agents emerge, there are key research opportunities that can potentially advance the field of anticoagulation safety further and for which federal resources could be leveraged. These unanswered questions are summarized in Figure 11.

Unanswered questions remain regarding warfarin pharmacogenomics

Pharmacogenomic testing for polymorphisms that affect warfarin dosing requirements is an area of recent interest regarding the optimization of warfarin therapy with regard to both safety and efficacy. Specifically, current dosing algorithms that incorporate pharmacogenetic considerations (e.g., http://www.warfarindosing.org) have shown to be less predictive among minority populations with regard to providing warfarin dose estimates [111]. Future research is needed to better understand causes for dose variation among minority populations; this may entail identifying additional polymorphisms that are specific to certain minority populations. Furthermore, to the extent that pharmacogenetic testing may allow providers to individualize warfarin dosing and monitoring algorithms based upon patients’ drug metabolism, more research is needed to determine the impact of such individualized algorithms on clinical outcomes and surrogate markers related to anticoagulant safety [112].

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

One area of future research that federal partners may be able to support relates to the need to identify the impact and reduce bleeding 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 pre-emptive 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 anti-platelet drugs, genomic polymorphisms, etc.).
Figure 11. 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**

*(CDC, AHRQ, FDA, public-private sector collaborations)*

- Identify barriers to anticoagulation clinic, PST/PSM utilization and factors that facilitate broader uptake of evidence-based anticoagulant ADE prevention strategies
- Identify factors that contribute to inter-clinic variability among anticoagulation clinic services (e.g., differences in patient risk profiles, targeting of excessively narrow INR target ranges, etc.)
- 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 based on 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 (incl. monitoring levels of anticoagulation, predicting effectiveness/risk)
- Address outstanding pharmacogenomic issues related to variance in warfarin-dose response
- Emerging pharmacogenomic issues related to new oral anticoagulants

**Abbreviations:** ADE = adverse drug event; INR = International Normalized Ratio; NOACs = new oral anticoagulants; PST = patient self-testing; PSM = patient self-management
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, 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, limit the wider use of NOACs [113]. Additionally, much remains to be learned about the 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 where federal partners could engage private sector stakeholders to facilitate ADE prevention strategies in relation to the NOACs. First, federal/private collaboration may be important to develop algorithms to facilitate selection of the optimal NOAC based on individualized/patient-centered risk/benefit assessments (e.g., history of previous exposure to anticoagulants, history of stable/un-stable INRs, co-morbidities, concomitant medications, pharmacogenomics, costs, 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), to develop and disseminate clinical guidance for providers regarding appropriate use of laboratory monitoring parameters to monitor NOAC effectiveness/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, and
- 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 [114]. 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).
References


82. Veterans Health Administration. [Citations from internal VHA data]. Unpublished data. 2008.


108. The White House. We the People. We petition the Obama Administration to: “Recognize pharmacists as health care providers!” Available from: [https://petitions.whitehouse.gov/petition/recognize-pharmacists-health-care-providers/3lkFWfwv](https://petitions.whitehouse.gov/petition/recognize-pharmacists-health-care-providers/3lkFWfwv).


Magnitude of the Problem

According to the 2011 CDC National Diabetes FACT Sheet [1], the national prevalence of diagnosed and undiagnosed diabetes mellitus (DM) among persons 20 years of age and older in 2010 was estimated to be about 25.6 million persons (or 11.3% of all persons in this age range). For those 65 years of age or older, the prevalence of diabetes is estimated to be 10.9 million persons, or 26.9% of all persons in this age group. It is estimated that about 95% of the 25.6 million individuals with diabetes have type 2 diabetes. Among adults diagnosed with either type 1 or type 2 diabetes, 12% take insulin only, 14% take both insulin and oral medication, 58% take oral medication only, and 16% do not take either insulin or oral medication [1].

It is recognized that not all diabetes agents cause hypoglycemia (e.g., Metformin). Thus, the term diabetes agents will be addressed as hypoglycemic agents. Because of inconsistent definitions in the literature, the FIW for Diabetes Agents ADEs have chosen to use the term serious hypoglycemia, recognizing that this terminology is not meant to represent any agency or scientific perspective. For the purpose of Action Plan, serious hypoglycemia was defined as requiring third party assistance (from family members and/or medical personnel), recognizing that there is a gradient of severity. Serious hypoglycemic events are recognized as an increasingly important public health issue potentially impacting millions of persons [2, 3, 4, 5, 6]. Several clinical trials, such as the 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), note an increase in the rate of severe/serious hypoglycemic events in the intensive control group compared to those assigned to the more generalized control group [7, 8, 9, 10, 11].
**Hypoglycemic agents are one of the drug classes most frequently associated with ADEs in both inpatient and outpatient settings**

**Inpatient Setting**

In a recent study of Medicare patients published by the Office of the Inspector General (OIG), ADEs represented one-third of all adverse events in hospitals. Hypoglycemia represented the third most common ADE reported \[12\]. Furthermore, nearly all cases of hypoglycemia were considered preventable. Rates of severe/serious hypoglycemia, defined as <40 mg/dL, were reported to be 0.4% of all non-ICU patient days \[13\], 1.9% among ICU-patient days \[13\], 2.3% of diabetic admissions \[14\], and 3-5% of hospitalized patients with diabetes \[15\]. The rate of hypoglycemia, defined as <50 mg/dL, was reported in three studies: 2.8% of all patient days \[16\], 1.8% of all hospitalized days \[17\], and 7.7% of admissions \[18\]. Additionally, on the basis of 25,145 hospital visits in the 2004 MPSMS sample, an estimated 10.7% of patients exposed to insulin/hypoglycemic agents experienced an ADE \[19\].

**Outpatient Settings**

Hypoglycemic agents (i.e., insulin and oral hypoglycemic agents) have been identified as two of the most common medication or medication classes associated with ED visits for ADEs among persons greater than 65 years of age \[20, 21\]. Between 2007 and 2009, insulin was implicated in an estimated 13.9% of emergent hospitalizations and oral hypoglycemic agents in 10.7% \[20\]. From 1999-2010, rates of hospital admissions for hypoglycemic events among Medicare beneficiaries increased by 22.3% while the rates of hospital admissions for hyperglycemia significantly decreased \[20\]. However, these data may underestimate the magnitude of the problem as most hypoglycemic event episodes are often treated in the ambulatory care setting \[21\]. Rates of severe/serious hypoglycemic events in ambulatory care requiring third party assistance are not known, but survey results suggest that they may be as high as 14% for oral agents and 59% for insulin \[22, 23\]. Additionally, studies have shown that higher frequencies of severe/serious hypoglycemic events were associated with lower socioeconomic status, duration of the disease \[24, 25\], and depression \[26\].

**Long-Term Care Settings**

No current data are available on the rate of hypoglycemic events among individuals residing in long-term care facilities. However, the primary risk factors for hypoglycemia (e.g., advanced age, recent hospitalization, and polypharmacy) are highly prevalent among nursing home patients \[27, 28\]. Data
from CMS indicates that approximately 33.4% of those receiving services in a certified nursing home have either type 1 or type 2 diabetes [29]. Currently only 1% of all skilled nursing facilities report data on adverse events to the CDC’s National Healthcare Safety Network (NHSN); however, this number is anticipated to increase over the next few years which will allow a better estimate of hypoglycemic events occurring in the long-term care setting [30].

There remains inconsistent application of minor and severe hypoglycemic events definitions across post-marketing and epidemiologic studies, thus making it challenging to compare hypoglycemic event studies.

Most recent large trials and the ADA have defined serious hypoglycemia as a situation requiring help from a third party (e.g. family member, paramedic, or emergency room visit). In contrast, mild episodes are classified as events that are self-treated. As a result of a lack of standardization in the definition and classification of hypoglycemia, documentation of the incidence in the literature is quite varied and incidence in those at highest risk is unknown [25, 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 [25, 31]. The ADA has defined documented symptomatic hypoglycemia as an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration $<=70$ mg/dl (3.9 mmol/l).

**Surveillance**

Definitions for hypoglycemia are variable, thus making comparisons between surveillance systems and the literature difficult. Currently available federal surveillance systems have the capacity to assess the national scope of hypoglycemic events. The systems involved in direct patient care (VA, IHS) can capture regional- and facility-level information on the quality of hypoglycemic event management. Examples of these systems are summarized in Table 7.
Table 7. Summary of Hypoglycemic ADE-related Metrics Collected by Currently-Available Federal Surveillance Systems

<table>
<thead>
<tr>
<th>Geographic Scope</th>
<th>Data Collection Methods</th>
<th>Hypoglycemic ADE or Management Metrics: Inpatient Setting</th>
<th>Hypoglycemic ADE or Management Metrics: Outpatient Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>National ADE Incidence</td>
<td>Administrative claims and/or EHR data</td>
<td>AHRQ (HCUP): Inpatient stays with ICD codes and E-codes</td>
<td>FDA (Sentinel Initiative, Mini-Sentinel): * ED visits, hospitalizations for hypoglycemic events</td>
</tr>
<tr>
<td>Medical record review</td>
<td>AHRQ (MPSMS): ** Inpatient stays with combination of laboratory triggers (e.g., glucose ≤ 50 mg/dl or glucose ≤ 70 mg/dl but &gt; 50 mg/dl) and clinical triggers (e.g., administrations of D 50)</td>
<td>CDC (NEISS-CADES): ED visits, emergent hospitalizations Algorithmic detection based on chart review of clinical charts to distinguish dose-related ADEs (hypoglycemia) due to diabetes agents from non-dose-related ADEs (such as allergic reactions); a mechanism code (unintentional overdose/supratherapeutic effect) may be used</td>
<td></td>
</tr>
<tr>
<td>Administrative data and survey data</td>
<td>AHRQ (NEDS): Derived from AHRQ’s state ED databases and from state inpatient database</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Used to estimate number of events (i.e., numerator data); ED visits with hypoglycemia as first-listed diagnosis were identified using a validated algorithm Estimates of the diabetic population from NHIS were used in the calculation of rates</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>National Health Interview Survey (NHIS) Used to calculate estimates of the population with diabetes (i.e., denominator) for calculation of rates</td>
<td></td>
</tr>
</tbody>
</table>
### Table 7. Summary of Hypoglycemic ADE-related Metrics Collected by Currently-Available Federal Surveillance Systems (continued)

<table>
<thead>
<tr>
<th>Geographic Scope</th>
<th>Data Collection Methods</th>
<th>Hypoglycemic ADE or Management Metrics: Inpatient Setting</th>
<th>Hypoglycemic ADE or Management Metrics: Outpatient Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>National, Regional-, Facility-level Spontaneous Reports</td>
<td>Voluntary reporting</td>
<td><strong>DOD (Patient Safety Reporting System)</strong>&lt;br&gt;▪ Any clinician-diagnosed or patient-reported ADEs&lt;br&gt;&lt;br&gt;<strong>FDA (FAERS):</strong>&lt;br&gt;▪ Any clinician-diagnosed or patient-reported ADEs&lt;br&gt;&lt;br&gt;<strong>VA (VA ADERS):</strong>&lt;br&gt;▪ Any clinician-diagnosed or patient-reported ADEs</td>
<td><strong>DOD (Patient Safety Reporting System)</strong>&lt;br&gt;▪ Any clinician-diagnosed or patient-reported ADEs&lt;br&gt;&lt;br&gt;<strong>FDA (FAERS):</strong>&lt;br&gt;▪ Any clinician-diagnosed or patient-reported ADEs&lt;br&gt;&lt;br&gt;<strong>VA (VA ADERS):</strong>&lt;br&gt;▪ Any clinician-diagnosed or patient-reported ADEs</td>
</tr>
<tr>
<td>Regional/ Facility-level ADE Incidence (+/- Rates)—Quality Improvement</td>
<td>Administrative claims and/or EHR data</td>
<td><strong>IHS (Resource and Patient Management System (RPMS-EHR))</strong>&lt;br&gt;▪ Adverse Reaction Tracking (ART) System entry related to a diabetes agent&lt;br&gt;▪ EHR entry in the Problem List of Hypoglycemia&lt;br&gt;&lt;br&gt;<strong>VA (Integrated Databases):</strong>&lt;br&gt;▪ ADE identified by ICD-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</td>
<td><strong>DOD (Pharmacovigilance Defense Application System):</strong>&lt;br&gt;▪ Outpatient clinic visits, ED visits, hospitalizations using relevant ICD-9 codes and/or CPT codes&lt;br&gt;&lt;br&gt;<strong>VA (Integrated Databases):</strong>&lt;br&gt;▪ ADE identified by ICD-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&lt;br&gt;&lt;br&gt;<strong>IHS Resource and Patient Management System (RPMS-EHR)</strong>&lt;br&gt;▪ Adverse Reaction Tracking (ART) System entry related to a diabetes agent&lt;br&gt;▪ EHR entry in the Problem List of Hypoglycemia</td>
</tr>
</tbody>
</table>

*Currently, FDA Sentinel initiative covers over 125 million lives which 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; ED = emergency department; EHR = electronic health record; HbA1c = hemoglobin A1c; ICD = International Classification of Diseases; ICD-CM = International Classification of Diseases, Clinical Modification; mg/dL = milligrams per deciliter; NHIS = National Health Interview Survey
In spite of the availability of current federal surveillance systems to help detect hypoglycemic events, several challenges remain. Many existing federal and private sector EHRs do not have integrated data systems which provide the comprehensive information necessary to define persons at risk for hypoglycemic events and enable precise categorization of numerators and denominators across the continuum of care. Additionally, existing metrics may need to be revised to improve accuracy, reliability, and clinical relevance. The development of more robust EHR systems will support the creation of new clinical quality measures and decision support tools, which will greatly improve the identification and management of patients with hypoglycemia.

**Effective surveillance of hypoglycemic events requires information on demographics, laboratory, pharmacy, and administrative claims data**

Few surveillance systems are able to provide information regarding hypoglycemic ADEs occurring as a result of care transitions. Additionally, few studies have validated the accuracy of diagnostic and procedural codes (International Classification of Diseases [ICD] codes, including Error [E]-codes) in capturing hypoglycemic events. As noted previously, there remains inconsistent application of minor and serious hypoglycemic events definitions across post-marketing and epidemiologic studies, thus making it challenging to compare hypoglycemic event studies.

**Increased reporting of these events in current national surveys along with use of standardized definitions will help advance the ability to track ADEs associated with hypoglycemic agents.**

Actions that can potentially advance surveillance strategies for hypoglycemic ADEs are summarized in Figure 12. National surveillance using population-based sampling or administrative claims data may be an efficient way of collecting nationally representative data on serious ADEs; however, reducing ADEs requires individual providers and patients to act at the point of care. Federal agencies and non-federal facilities that provide care play a role in facilitating the infrastructure necessary for smaller units (i.e., regional, facility, ambulatory care centers) to monitor ADEs.

The National Health Interview Survey (NHIS) may provide an opportunity for surveillance. The CDC’s National Center for Health Statistics (NCHS) collects information from NHIS annually via household interviews designed to help monitor the health of the U.S. population. Additional information collected within the ambulatory setting could be used to measure the frequency of serious hypoglycemic events.
Figure 12. Federal Interagency Workgroup Recommendations for Actions that Can Potentially Advance Surveillance Strategies for Hypoglycemic ADEs

**Actions that Can Potentially Advance Surveillance Strategies for Hypoglycemic ADEs**

- **Address gaps in standard surveillance definitions for hypoglycemic events**
  - Clearly define both severe/serious and mild hypoglycemic events
  - Use retrospective medical review to minimize opportunities for bias or misclassification

- **Assess the adequacy of diagnostic and procedural coding for capturing hypoglycemic events**
  - Assess specificity, sensitivity, PPV, and NPV of ICD and CPT codes for capturing hypoglycemic events
  - Consider refinement of existing quality measures or development of new quality measures to improve accuracy, reliability, and clinical relevance

- **Coordinate efforts across federal government and with private sector to enhance inpatient monitoring**
  - Refine Common Formats for reporting specific ADEs

- **Improve access to more integrated EHR data linked to pharmacy, laboratory, and outcomes data**

- **Improve efforts to collect additional information within the ambulatory setting. Management of hypoglycemic events in the home, school, workplace, and long term care settings may reduce subsequent events that require emergency room visits or hospitalizations**
  - Incorporate well accepted survey questions into the Medicare Current Beneficiary Survey (MCBS), the National Health and Nutrition Survey (NHANES), and/or the National Health Interview Survey (NHIS) to obtain weighted population-based estimates

**Abbreviations:** ADEs = adverse drug events; 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 [32, 33] and American Geriatric Society [34], as well as the VA [35] and DOD [35] formally recommend individualization of target glycemic goals based upon life expectancy, comorbid conditions, social support, and personal preference. The American Geriatric Society, 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% in most persons over 65 is not warranted. This recommendation is based on the potential of harms (relative to benefit) noted when patients have major co-morbid conditions or limited life expectancy [36, 37].

Evidence-based professional and public education resources offer guidance on individualizing treatment recommendations. Table 8 presents some of these resources.

Table 8. Evidence-based Professional and Public Education Resources on Individualizing Treatment for Diabetes

<table>
<thead>
<tr>
<th>Professional Education Resources</th>
<th>Public Education Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>The American Geriatrics society &amp; Choosing Wisely</td>
<td>Ask the Expert - Glycemic Control</td>
</tr>
<tr>
<td>AGS Education &amp; Clinical Resources on Diabetes</td>
<td>Healthinaging.org: Diabetes</td>
</tr>
<tr>
<td>Diabetes in Older Adults: A Consensus Report</td>
<td></td>
</tr>
</tbody>
</table>

Inpatient Settings

Appropriate glycemic control in the inpatient setting requires a careful balance of managing the risks associated with both hyperglycemia and hypoglycemia. Although uncontrolled hyperglycemia is consistently associated with poor outcomes in a dose/response relationship from epidemiological studies, the use of very tight glucose control through intensive insulin therapy (IIT) has shown mixed results from clinical trials [38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55]. Single

\[\text{http://www.americangeriatrics.org/health_care_professionals/clinical_practice/clinical_guidelines_recommendations/choosingwisely}\]

\[\text{http://www.americangeriatrics.org/diabetes080312}\]


\[\text{http://www.healthinaging.org/aging-and-health-a-to-z/topic:diabetes/}\]
site randomized trials demonstrated a reduction in mortality and sepsis in ventilated ICU (mixed surgical and non-surgical) patients through the use of Intensive Insulin Therapy [50]. However, these results were not replicated in a large, multicenter trial (the NICE-SUGAR Study), where serious hypoglycemia was increased in the IIT arm and associated with increased mortality [51]. Professional society recommendations for the upper level for glycemic targets in the ICU setting range from 150 mg/dl (SCCM) to 200 mg/dl (American College of Physicians).

The risk for hypoglycemic events may be increased due to numerous patient and iatrogenic factors. Iatrogenic factors include the use of insulin and/or oral hypoglycemic agents too aggressively, inappropriately, or without sufficient follow-up in the hospital setting. They also include unexpected interruption of nutritional intake (decreased oral intake, discontinuation of enteral feeding, discontinuation of intravenous glucose solutions or TPN, sudden NPO status, and unexpected transport from the unit). Prior iatrogenic hypoglycemic events have been shown to be a strong predictor of recurrence. Hypoglycemic events also can result if there are additional changes in a patient’s drug regimen that alter insulin resistance (e.g., corticosteroids) or the metabolism of hypoglycemic agents [56, 57, 58]. Table 9 addresses some of the patient and iatrogenic factors.

Table 9. Patient and Iatrogenic Risk Factors for Hypoglycemic Events

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>Iatrogenic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low BMI</td>
<td>The use of insulin and/or oral hypoglycemic agents too aggressively, inappropriately, or without sufficient follow-up in the hospital setting.</td>
</tr>
<tr>
<td>Cachexia</td>
<td>Unexpected interruption of nutritional intake (decreased oral intake, discontinuation of enteral feeding, discontinuation of intravenous glucose solutions or TPN, sudden NPO status, and unexpected transport from the unit)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>Advanced malignancy</td>
<td></td>
</tr>
<tr>
<td>Advanced liver disease</td>
<td></td>
</tr>
<tr>
<td>Advanced renal disease</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI = body mass index; TPN = total parenteral nutrition

The use of oral agents, failure to adjust diabetes regimens in response to decreases in oral intake, and unexpected deviation from normal hospital routines have been some of the most common iatrogenic

---

1 It should be noted that the outcomes may be related to the way in which blood glucose was assessed and to the cohesiveness of staff training.
factors [58]. Unexpected interruption of tube feedings or other sources of nutrition, and failure to respond appropriately to an initial hypoglycemic event are among the most common, and potentially most preventable, sources of iatrogenic hypoglycemic events. The top predictors for iatrogenic factors are as follows: nutritional interruption, prior hypoglycemic events, and lack of clinical decision support [58]. Recent literature highlights poor adherence to hypoglycemic agent treatment and documentation standards [58]. Studies have shown that more than 40% of patients who experience one iatrogenic episode go on to suffer at least one additional distinct hypoglycemic event which is largely preventable [58].

These iatrogenic factors and patient risk factors should be addressed using professional judgment. Available evidence supports the treatment of hyperglycemia during hospitalization in both patients with and without the diagnosis of diabetes. Intensive insulin therapy, in the way it has been practiced by most health care providers, does not reduce mortality and may increase risk for severe hypoglycemic events, although it may reduce infection rates [41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58].

ISMP has identified insulin as an inpatient high-alert medication [59]. Data indicate that approximately one quarter of all patient safety incidents involving insulin resulted in patient harm and insulin may be implicated in 33% of all medication error-related deaths [59, 60, 61, 62, 63, 64]. 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 [59, 60, 61, 62, 63, 64].

A multi-factorial risk mitigation approach to the prevention of hypoglycemic events is encouraged, including nutritional intake, prior hypoglycemic events, multidisciplinary efforts to increase the frequency of monitoring, appropriate adjustment of antihyperglycemics medication, and/or increase carbohydrate supply. Additionally, proactive adjustments of the monitoring and treatment regimens of patients’ with hypoglycemic events versus traditional retrospective analysis are encouraged.

Currently, there are efforts underway to evaluate the effectiveness of bundled approaches to reduce the prevalence of hypoglycemic events in the inpatient setting. One Medicare funded effort is the Partnership for Patients (PfP). PFP is currently testing the scaling of prevention strategies for
hypoglycemic event prevention in the inpatient setting through the hospital engagement networks (HENs). While the system used a multiphase approach, the bundled elements to decreasing hypoglycemic events included:

- Adopting a basal/bolus insulin protocol,
- Instituting an RN driven protocol for hypoglycemia, and
- Ensuring the coordination of mealtime blood sugar testing, insulin administration, and meal consumption.

A summary of existing prevention strategies/tools that address safe and effective management of hypoglycemic events are summarized in Figure 13.

Figure 13. Current and Potential Approaches Related to the Prevention of Hypoglycemic Events—Inpatient Settings

<table>
<thead>
<tr>
<th>Systems Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systems to promote safe and appropriate use of basal, prandial and corrective insulin might include [59, 60, 61, 62, 63, 64]:</td>
</tr>
<tr>
<td>- Education of hospital based health professionals, as this has been associated with decreased prescribing errors</td>
</tr>
<tr>
<td>- Reduce prescribing errors through the development of forcing functions in computerized health records to make it easier to correctly manage glucose with protocols and order templates for insulin in diabetic patients, and to convert from subcutaneous insulin in those patients previously not requiring insulin.</td>
</tr>
<tr>
<td>ISMP has reported numerous cases in which U-500 insulin was inadvertently interchanged with U-100 insulin, resulting in fivefold dosing error.</td>
</tr>
<tr>
<td>- Eliminate storage of U-500 insulin in patient care areas</td>
</tr>
<tr>
<td>- Store U-100 insulin in a secure fashion segregated from other medications.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendations for safe use of insulin in hospitals, a joint project of the American Society of Health System Pharmacists and the Hospital and Health System Association of Pennsylvania.¹</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-disciplinary coordination across all phases of medication use process</td>
</tr>
<tr>
<td>Adjustments in response to changes in oral intake</td>
</tr>
<tr>
<td>Timely response to initial events</td>
</tr>
<tr>
<td>Adjustments for deviations to normal routine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Attention to Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentation of oral intake</td>
</tr>
<tr>
<td>Coordination of meal time blood sugar testing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Use of Protocols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal/bolus insulin protocol</td>
</tr>
<tr>
<td>RN driven protocol</td>
</tr>
</tbody>
</table>

Figure 13. Current and Potential Approaches Related to the Prevention of Hypoglycemic Events—Inpatient Settings (continued)

**Use of Order Sets**

One way to standardize management of hypoglycemic events is with use of template order sets that provide prescribing support such as those developed by some hospitals in the Veterans Health Administration. The VA reports both hypo- and hyperglycemia rates in intensive care unit (ICU) patients. This data is publicly reported [47, 48].

**Resources for Communication and Care Coordination**

- **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)

Opportunities for advancing hypoglycemic ADE prevention strategies/tools in inpatient settings are summarized in **Figure 14**.

**Figure 14. Opportunities for Advancing Hypoglycemic ADE Prevention Strategies/Tools as Identified by the National Quality Strategy Priorities—Inpatient Settings**

- Adjust medication in response to changes in oral intake
- Assess prior cause(s) of hypoglycemic events and aggressively avert recurrent hypoglycemic events
- Respond timely to adverse events
- Make adjustments for deviation in normal routine
- Document oral intake
- Coordinate meal time and blood sugar testing
- Use quality measures to identify hypoglycemic events
- Implement protocol-driven and evidence-based order sets that permit prescribing of complex insulin regimens and eliminate the use of free-text insulin orders in electronic and paper medical records

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2. For ICU patients, this dashboard reports quarterly, the proportion of patient days on hypoglycemic events agent with any hypoglycemic events event (glucose ≤ 45 mg/dL and/or ≤ 60 mg/dL) and the proportion of patients on hypoglycemic events agents with a mean glucose in the > 180mg/dL as well as risk adjusted outcomes [47, 48]. Efforts are supported by a SharePoint site that includes the VA/DOD guidelines, templated order sets to manage hyperglycemia and hypoglycemic events, references, protocols, a special section on reducing hypoglycemic events and educational materials.
Figure 14. Opportunities for Advancing Hypoglycemic ADE Prevention Strategies/Tools as Identified by the National Quality Strategy Priorities—Inpatient Settings (continued)

**Patient and Family Engagement**
- Individualized target setting
  - Acknowledgement of patient risk factors (BMI, cachexia, age, CHF, advanced malignancy, renal, or liver disease)
  - Understand iatrogenic factors (change in nutritional intake, patient compliance, regimen change)
- Educate patients on any changes to insulin regimen
- Educate patients on use of products for treating low blood glucose, such as over-the-counter products for treating low blood glucose

**Effective Communication and Coordination of Care**
- Multidisciplinary coordination throughout medication process [65, 66, 67, 68, 69]
- Address fragmentation of medical care
- Educate providers on:
  - Use of insulin associated with decreased prescribing errors
  - Mononumeric insulins sensitive to temperature changes
  - Root causes of hypoglycemic events

**Science-driven Prevention and Treatment**
- Consider individual characteristics
- Use protocols to:
  - Assess risk during initial evaluation
  - Reassess risk periodically
- Assess cause of prior events
- Ensure consistency in order sets
- Use standardized, evidence based order sets (avoid free text)
- Conduct root cause analysis of all hypoglycemic events
- Capture critical information at time of hospital admission:
  - Prior history of diabetes or hyperglycemia
  - Past management of hyperglycemia
  - Level of glycemic control
  - Assessment of patient’s cognitive abilities, literacy level, visual acuity, dexterity, cultural context, and financial resources for acquiring outpatient diabetic supplies

**Promote Best Practices within Communities**
- Encourage multidisciplinary care coordination [24, 36]
- Consider individual patient circumstances (e.g., cognition, life expectancy, sedation) [24]
- Ensure professional supervision during any medication changes

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

Medication errors and ADEs have been linked to poor communication of instructions to the patient at the time of discharge [65, 66, 67, 68, 69]. This is particularly true for insulin regimens, which are inherently more complex. Because the day of discharge is not always conducive to retention of verbal instructions [65, 66, 67, 68, 69], clear written instructions provide a reference for patients and their outpatient providers, and provide 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 to a generic hospital discharge form [65, 66, 67, 68, 69].

To assist with medication reconciliation during the transfer from inpatient to outpatient settings and to avoid post discharge adverse events/complications that can result in readmission, AHRQ’s Medications At Transitions and Clinical Handoff (MATCH) toolkit of medication reconciliation is a potential tool that can be used to help facilitate medication reconciliation during transitions of care.1

The ADA recommends a transition to outpatient care that includes a team approach involving physicians, nurses, pharmacists, medical assistants, dietitians, case managers, and social workers. The recommended transition of care begins with hospital admission assessments that include:

- 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 allows sufficient time to prepare the patient [24, 36]

Additionally, the literature recommends that the following areas be reviewed and addressed before the patient is discharged from the hospital:

- Level of understanding related to their diagnosis of diabetes
- Self-monitoring of BG and explanation of home BG goals
- Definition, recognition, treatment, and prevention of hyperglycemia and hypoglycemic events
- Identification of health care provider who will be responsible for diabetes care after discharge
- Information on consistent eating patterns

Directions on when and how to take BG-lowering medications, including administration of insulin (if the patient is receiving insulin for ongoing management at home)

- Sick day management
- Proper use and disposal of needles and syringes [65, 66, 67, 68, 69]

**Outpatient Settings**

Given the complexity of the patient population of those at highest risk of experiencing hypoglycemic events (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 because it uses a systematic approach to restructuring medical care to create partnerships between health systems and communities [70, 71, 72]. To improve chronic illness care, the model includes system requirements for health care organizations, community resources, self-management support, delivery design, decision support, and clinical information.

“Shared decision-making,” which engages the patient, is an essential element of ongoing care. The collaborative goal setting and problem solving result in a shared health care and management. In order to participate in decisions related to his/her illness in the context of his/her belief systems and culture, the patient must have sufficient information which he/she clearly understands. Patients need to be both “informed” and “activated”. As such, provider education should emphasize cultural competency, health literacy/numeracy, shared decision-making practices, and motivational interviewing [70, 71, 73, 74].

A key element of any strategy to reduce the risk of hypoglycemic events is recognizing the importance of existing co-morbid conditions which may impact adherence and risk of medication side effects as well as impact physical function and quality of life. Type 1 (T1DM) or Type 2 (T2DM) diabetes is a chronic disease. Management for the broad categories of diabetes will not be the same because of the differences in underlying etiology and the demographics of the affected populations, as well as time from diabetes diagnosis. Co-morbid conditions are more common in patients with T2DM, particularly as they age [72, 75, 76, 77]. According to the Medical Expenditure Panel Survey, most adults with diabetes have at least one co-morbid chronic disease and as many as 40% have at least three [72, 75, 76, 77]. Some co-morbid conditions (e.g., hypertension, hyperlipidemia, peripheral sensory neuropathy, macrovascular/hypertensive renal disease, and cardiovascular disease) are directly related to the metabolic disorder underlying T2DM. Other co-morbid conditions are the sequelae of hyperglycemia.
(e.g., proliferative retinopathy [but not macular edema] and microvascular renal disease). T2DM itself may be secondary to weight gain or physical inactivity associated with other chronic disease conditions unrelated to diabetes per se. Lastly, throughout the aging process, individuals are at increased risk for co-morbid disease independent of diabetes [72, 75, 76, 77], which may complicate diabetes management and increase morbidity and mortality in persons with diabetes.

Self-management of glycemic control 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 room visits or hospitalizations. Patient self-management may be impacted 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 impacting the ability to maintain a healthy lifestyle, including exercise, good dietary habits, and adherence to a prescribed regimen [78, 79, 80].

Health systems and providers seeking to improve diabetes management and prevention of hypoglycemic events must consider a more holistic, patient-centered approach [32, 33, 34, 35, 36, 37]. Previous outpatient prevention tools for hypoglycemic events have lacked (1) explicit recognition of chronic co-morbid conditions as an additional, important level of complexity, and (2) use of a framework that identifies contributing risk factors and converts them into a set of specific, actionable strategies that can be broadly implemented. Using this framework would allow for identification of gaps in achieving improved care.

Professional and federal guidelines recommend the education of patients and families 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 [24, 32, 33, 34, 35, 36, 37]. **Figure 15** outlines existing tools, studies, and nationally recognized guidelines that may help in the management of diabetes and the prevention of ADEs associated with diabetes agents. Patient and caregiver understanding of care management (health literacy and numeracy) are also critical to avoiding ADEs.
Figure 15. Current and Potential Approaches Related to the Prevention of Hypoglycemic Events—Outpatient Settings

<table>
<thead>
<tr>
<th>Education Resources for Patients and Family Members</th>
</tr>
</thead>
</table>
| • Medicines for Type 2 Diabetes: A Review of the Research for Adults  
  AHRQ Publication No. 11-EHC038-A  
  Reviews the research on the benefits and possible side effects of medicines to lower or control blood sugar  
| • Methods for Delivering Insulin and Monitoring Blood Sugar: A Review of the Research for Children, Teens and Adults with Diabetes  
  AHRQ Publication No. 12-EHC036-A  
  Discusses evidence regarding ways to measure blood sugar and take insulin  
| • Premixed Insulin for Type 2 Diabetes: A Guide for Adults  
  AHRQ Publication No. 08(09)-EHC017-A  
  Compares benefits, side effects, and costs of types of insulin and pills for diabetes  

<table>
<thead>
<tr>
<th>Resources for Look-Alike, Sound-Alike Medications [81, 82]</th>
</tr>
</thead>
</table>
| The Joint Commission and the World Health Organization noted “that while many look alike, sound alike (LASA) errors occur in hospitals, the problems are at least as great in outpatient care settings, which require the same degree of rigor in implementing risk reduction strategies”.  
  [http://www.jointcommission.org/LASA](http://www.jointcommission.org/LASA) |
| A list of risk reduction strategies which can be recommended for use by retail pharmacies, ambulatory clinics, and inpatient providers  

<table>
<thead>
<tr>
<th>Resources for Children &amp; Teens</th>
</tr>
</thead>
</table>
| Resources for management of diabetes in younger populations  

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4. Look Alike Sound Alike Medications were identified as a Joint Commission on Accreditation of Healthcare Organizations National Patient Safety Goal (NPSG) in 2005. For example the NPSG has identified that Humalog has been confused with Humalin. A list of such medications, including insulin preparations is available at [http://www.jointcommission.org/LASA](http://www.jointcommission.org/LASA).
Figure 15. Current and Potential Approaches Related to the Prevention of Hypoglycemic Events—Outpatient Settings (continued)

Resources from American Diabetes Association (ADA)
The ADA has noted the following general recommendations for care of Older Adults with Diabetes on hypoglycemic agents [24, 36]:

- For Diabetes Self-Management Education (DSME) in older adults, consider sensory deficits, cognitive impairment, and different learning styles, use different teaching strategies, and include caregivers.
- Develop and update an individualized treatment plan, screen older adults periodically for cognitive dysfunction, functional status, and fall risk using simple tools such as those at http://www.hospitalmedicine.org/geriresource/toolbox/determine.htm.
- Assess for hypoglycemic events regularly by asking patient and caregiver about symptoms or signs and review blood glucose logs. In patients with type 2 diabetes, risk of hypoglycemic events is linked more to treatment strategies than to achieved low HbA1c (e.g., a patient with a low HbA1c on metformin alone has a lower risk of hypoglycemic events than a patient with a high HbA1c on insulin).
- If recurrent or severe hypoglycemic events occur, strongly consider changing therapy and targets.
- Assess the burden of treatment on older adult patients (caregivers), consider patient/caregiver preferences, and attempt to reduce treatment complexity.

Addressing Transition of Care
The new Re-Engineered (RED) Toolkit uses health literacy and culturally competent patient education and discharge processes.¹

The most recent private sector and federal guidelines recommend individualized targets based upon life expectancy and chronic co-morbid conditions.

*Shared decision-making, in which patient preference should be taken into account, is appropriate in clinical settings where there is no single or ideal diagnostic or treatment regimen.*

Several medical associations endorse shared decision-making [73, 74]. For example, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) June 2012 position statement advocates shared decision making with the patient when choosing goals of therapy [74].

Opportunities for advancing hypoglycemic ADE prevention strategies/tools in outpatient settings are summarized in Figure 16.

¹ http://www.ahrq.gov/professionals/systems/hospital/toolkit/
Figure 16. Opportunities for Advancing Prevention of Hypoglycemic Events Strategies/Tools as Identified by the National Quality Strategy Priorities—Outpatient Settings

### Safer Care

- Medication adjustments in response to changes in oral intake
- Coordination of meal time and blood sugar testing
- Care coordination across all providers
- Medication reconciliation

### Patient and Family Engagement

- Tools to establish individual patient goals
- Shared decision making including patient preference (recommended by ACA)
  - Example of shared decision-making tool from the VA
- Teach back method
  - Guidance on how to use the teach back method can be found in Tool 5 of the Health Literacy Universal Precautions Toolkit
- Train health care professionals on how to address cultural competency
  - The newly enhanced National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care: A Blueprint for Advancing and Sustaining CLAS Policy and Practice
- Train health care professionals on how to address health literacy
  - The Joint Commission has issued a position paper that outlines “Attributes of a Health Literate Organization”
  - The Institute of Medicine published a discussion paper that describes the “Ten Attributes of Health Literate Health Care Organizations”
- Education of patients on use on products for treating low blood glucose

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1 Section 3506 of the Affordable Care Act encourages greater use of shared decision-making in health care. It funds an autonomous program that would develop standards for and certify patient decision aids. These decision aids are intended to provide evidence data on the risks, benefits, effectiveness, and cost of various diagnostic tests and therapeutic interventions it would also facilitate the development and evaluation of evidence-based decision aid tools through the Department of Health and Human Services (HHS) funded grants and contracts. The Center for Medicare and Medicaid Innovation (CMMI) (part of The Centers for Medicare & Medicaid Services and HHS) is also authorized to evaluate decision-making models. Tools that demonstrate cost savings or improvement in the quality of life can be mandated for implementation throughout Medicare. HHS grants to health care providers would provide training and technical support for use of these decision aids.

ii [http://www.healthquality.va.gov](http://www.healthquality.va.gov)

iii [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4057371/pdf/10.1371_1](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4057371/pdf/10.1371_1)

iv [https://www.thinkculturalhealth.hhs.gov/Content/clas.asp](https://www.thinkculturalhealth.hhs.gov/Content/clas.asp)


vi [http://www.jointcommission.org/assets/1/6/10attributes.pdf](http://www.jointcommission.org/assets/1/6/10attributes.pdf)

vii [http://iom.edu/Global/Perspectives/2012/HealthLitAttributes.aspx](http://iom.edu/Global/Perspectives/2012/HealthLitAttributes.aspx)

### Effective Communication and Coordination of Care

- Provider training on effective use of decision aides
- E-Learning material (e.g., videos, electronic educational tools)
- Health care professionals should be encouraged to ask their patients if they experience any issues with nutrition, and dietitians are encouraged to be part of this process.
- Medication reconciliation at the time of hospital discharge has been a Joint Commission Patient Safety Standard [90] and is also a critical element of care in ambulatory care, as many patients with diabetes receive prescriptions from more than one outpatient provider.
- Patient education
  - Check 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 inaccuracy of self-monitoring equipment

### Science-driven Prevention and Treatment

- Development and enhancement of decision aides
- Provider coordination of any changes in medication
- Addressing inaccuracy of self-monitoring of blood glucose [ii] with patients and caregivers [91, 92, 93, 94]
- Addressing inaccuracy of HbA1c variance or bias [iii, iv] Information can be found at [91, 92, 93, 94]

### Promote Best Practices within Communities

- Multidisciplinary care coordination [32, 33, 34, 35, 36, 37]
- Consideration of individual patient circumstances (e.g., cognition, life expectancy, sedation) [32, 33, 34, 35, 36, 37]
- Professional supervision during any medication changes

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[ii] The acceptable accuracy of these devices permitted by FDA ± 15 mg/dL of the results of the reference measurement at glucose concentrations < 75 mg/dL or ± 20% at glucose concentrations > 75 mg/dL [94]. ISO permits plus or minus 15 mg/dl for values less than 75 mg/dl. Accuracy varies among meters, and addition error can be introduced by user parameters. These issues have recently been reviewed by the Federal Drug Administration. [91, 92, 93, 94]

[iii] The current CAP limit of total error is ±7% which corresponds to ±0.5% HbA1c at 7% HbA1c. Over 95% of clinical laboratories meet or exceed this threshold; however, most point of care instruments do not. The question has been raised NGSP meetings (ngsp.org) as to whether or not this degree of total error can lead to incorrect treatment decisions at the individual level. The issue was also reviewed by the congressionally legislated Diabetes Mellitus Interagency Coordinating Committee meeting in 2011 ([http://www2.niddk.nih.gov/AboutNIDDK/CommitteesAndWorkingGroups/DMICC/DMICCMetingonMarch112011.htm](http://www2.niddk.nih.gov/AboutNIDDK/CommitteesAndWorkingGroups/DMICC/DMICCMetingonMarch112011.htm)) entitled Diabetes: A1c Questions/Diagnosis A Report of the Diabetes Mellitus Interagency Coordinating Committee.

Incentives and Oversight

Incentives and Oversight Opportunities (Section 3) of this Action Plan provides a comprehensive overview of the existing federal incentives and oversight resources that may be leveraged moving forward to help reduce the incidence of severe hypoglycemic events. The discussion that follows outlines incentives and oversight opportunities specific to diabetes.

Health Information Technology (HIT)

*The FIWs for ADEs have proposed EHR (Stage 3) Meaningful Use requirements that can potentially advance hypoglycemic ADE prevention*

The FIW for hypoglycemic ADEs discussed and identified various health care quality measures specific to hypoglycemic safety that were amenable for incorporation into EHR-based quality measure strategies. The FIW recommended the measures (Table 10) to the HHS Office ONC for consideration as possible candidate measures for Stage 3 EHR MU requirements that can potentially support hypoglycemic ADE prevention and monitoring.
### Table 10. EHR (Stage 3) Meaningful Use Requirements that Can Potentially Advance Hypoglycemic ADE Prevention as Proposed by the Federal Interagency Workgroup (FIW) for ADEs

<table>
<thead>
<tr>
<th>Meaningful Use Requirement</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quality Measure Concept</strong></td>
<td><strong>Explanation</strong></td>
</tr>
</tbody>
</table>
| Eligible Providers         | Overtreatment measure: Percent of patients on sulfonylurea/insulin therapy with out-of-range HbA1c (Patients on sulfonylurea or insulin therapy with chronic co-morbid conditions and/or age >65 and HbA1c <7)  
  **Chronic co-morbid conditions:** Cognitive impairment/dementia; advanced microvascular diabetes complications, limited life expectancy, current substance use |
| **Clinical Decision Support (CDS) Recommendations—Eligible Providers** | |
| Alert to potential risk for hypoglycemic events | When there is a high risk patient, the provider should be alerted that there is a potential for risk and take action OR state the reason why there was no action taken. |
| Shared Decision-making between physician and patient on target HbA1c values | Target HbA1c value should be entered in a field based on shared decision-making between the physician and patient. |
| Patient Centered Action Plan | Appropriate steps should be taken after physician alerted to patient risk factors for hypoglycemic events. |
| Flow Sheet | Flow sheet with certain elements should be presented on a single page to the physician |
| **Patient List Recommendation—Eligible Providers** | |
| Stratify by HbA1c value and Co-morbid conditions | EHRs incorporate patient list features which allow clinicians to stratify individuals who are currently receiving hypoglycemic events agent’s therapy by their HbA1c value and certain co-morbid conditions. |
| **Quality Measure Concept** | **Explanation** |
| Eligible Hospitals         | Hypoglycemic events, Serious: The rate of hypoglycemic events following the administration of an hypoglycemic agent |
| Hyperglycemia              | Average percentage of hyperglycemic hospital days for individuals with a diagnosis of diabetes mellitus, anti-diabetic drugs (except metformin) administered, or at least one elevated glucose level during the hospital stay  
  Note this measure is listed as a companion balancing measure to the hypoglycemia measure. |
Table 10. EHR (Stage 3) Meaningful Use Requirements that Can Potentially Advance Hypoglycemic ADE Prevention as Proposed by the Federal Interagency Workgroup (FIW) for ADEs (continued)

<table>
<thead>
<tr>
<th>Meaningful Use Requirement</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Measure Concept Recommendation—Eligible Hospitals (continued)</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia, Mild</td>
<td>Monitored days in which any hypoglycemic event (&lt;70 mg/dL) reported</td>
</tr>
<tr>
<td>Recurrent Hypoglycemia</td>
<td>Patients suffering at least one recurrent hypoglycemic event on a subsequent hospital day during the same hospital stay.</td>
</tr>
<tr>
<td>EHR Functionality/Usability Recommendation—Eligible Hospitals</td>
<td></td>
</tr>
<tr>
<td>Reporting of hypoglycemic events etiology and action to mitigate hypoglycemic events</td>
<td>When there is a patient who has a BG value of &lt;70 mg/dl, an assessment of the etiology should be documented, and factors that could lead to repeated events addressed.</td>
</tr>
<tr>
<td>Alert to potential risk for hypoglycemic events</td>
<td>When there is patient who has experienced repeated (more than 2 readings) blood glucose value of &lt; 70 mg/dl, the provider should be alerted that there is a potential for risk and take action OR state the reason why there was no action taken.</td>
</tr>
<tr>
<td>Flow Sheet</td>
<td>Pertinent information should be available to the physician in an easy to read, one page format.</td>
</tr>
<tr>
<td>EHR Functionality/Usability Recommendation—Diabetes Agents</td>
<td></td>
</tr>
<tr>
<td>Health literacy</td>
<td>Ability to provide patient education materials on high risk medications that follow health literacy principles and meet language needs and confirm understanding.</td>
</tr>
<tr>
<td>Health numeracy</td>
<td>Assessment for poor understanding of numeric information critical to persons with diabetes self-management to avert potential harms.</td>
</tr>
</tbody>
</table>

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

**Research (Unanswered Questions)**

As the prevention of hypoglycemic events evolves, key research opportunities have the potential to further advance the field of hypoglycemic event safety. These questions relate to provider education, patient education, surveillance, incentives and oversight, and health systems. The unanswered research questions are summarized in Figure 17.
Figure 17. Federal Interagency Workgroup Recommendations for Actions that Can Potentially Advance Research Strategies for Hypoglycemic ADE Prevention

**Actions that Can Potentially Advance Research Areas for Hypoglycemic Event Safety**

**Provider education (CDC, AHRQ, FDA, public-private sector collaborations)**
- Research how co-morbid conditions affect hypoglycemic events
- Investigate provider decision making with regards to balancing benefits and harms when prescribing medications
- Research how to change physician behavior and acceptance of principles of individualizing care and shared decision-making
- Investigate different packaging can prevent medication errors

**Patient/caregiver education (CDC, AHRQ, FDA, public-private sector collaborations)**
- Research on the impact of individualized education material
- Evaluate impact of increased health literacy and numeracy and the prevention of hypoglycemic events

**Surveillance (CDC, AHRQ, FDA, public-private sector collaborations)**
- Research rates of severe hypoglycemic events in ambulatory care settings stratified by education level, health literacy, age, and co-morbid conditions
- Use survey data to analyze rates of hypoglycemic events in ambulatory care setting
- Evaluate impact of hypoglycemic events on quality of life

**Incentive & Oversight (CMS)**
- Consider a measure of overtreatment using hypoglycemic agents
- Examine impact of quality measure exclusion criteria on rates of hypoglycemic events

**Health Systems**
- Research how current prevention tools impact transitions of care
References


**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 non-cancer pain (CNCP). Acute and chronic pain affects many Americans every year. Chronic pain alone is reported by over 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 CNCP is more controversial due to the limited evidence surrounding the safety and efficacy of long-term opioid use for CNCP [2]. Nonetheless, opioids are recommended for treatment of CNCP in clinical practice guidelines as a treatment option when used judiciously 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 has roughly doubled and the sales rate of prescription opioids (in kg/10,000 pop) has increased four-fold [4], with an estimated 201.5 million opioid prescriptions dispensed in 2009 [5]. In 2009, hydrocodone, a prescription opioid, was the single most commonly prescribed medication in the US and opioid analgesics were the third most commonly prescribed class of medications overall leading the U.S. 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 and it is not clear that the dramatic increase in the use of opioids has led to improved treatment of pain overall, especially in CNCP [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 can include oversedation and respiratory depression; gastrointestinal adverse events such as nausea, vomiting and constipation; hyperalgesia; pruritus; and immunological and hormonal dysfunction [9]. Although all of these ADEs were discussed and considered by the Federal Interagency Workgroup (FIW) for Opioid ADEs as important possible targets of the Action Plan, highest priority was given to ADEs resulting from unintentional opioid overdoses (e.g., oversedation, respiratory depression) due to the severity of their impact in terms of associated mortality and morbidity. Opioid overdoses constitute a tremendous public health burden that is potentially amenable to measurable prevention efforts and could benefit from a coordinated National Action Plan.

**Prescription opioid overdoses are considered to be one of the nation’s leading preventable public health problems**

Opioid overdose has come into the national spotlight as a significant cause of drug related injury and an important cause of adverse drug events. Opioids have been included in the 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 is greater than overdose deaths involving heroin and cocaine combined [10]. This represents an over 300% increase from just over 4,000 prescription opioid overdose deaths in 1999 [10]. Moreover, the number of emergency department (ED) visits related to opioid misuse and abuse has more than doubled since 2004 to over 420,000 ED visits in 2011 [12]. Prescription opioid abuse is estimated to result in over $72 billion dollars in healthcare-related costs each year [13].

**The under treatment of pain remains an important problem in the US—Efforts to minimize the burden of harms from opioids have to be implemented in parallel with efforts that ensure patients suffering from pain receive the most effective and safest available treatment**

All recommendations in this Action Plan should always be taken in the context of improving overall patient care through providing the safest and most effective, evidence-based treatments. In pain care, clinical decisions require a careful balance of the effectiveness of various pain treatments and the safety and risks of the treatment provided. Therefore, these recommendations recognize the importance of the clinician judgment in making these decisions.
Because the dramatic increase in the use of opioids over the past decades is largely attributed to use for CNCP, the outpatient recommendations for safer opioid use will focus on long-term opioid use for CNCP, though the recommendations are likely to be applicable for promoting the safety of opioids for any indication.

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

The misuse and abuse of opioids are important public health problems and are the current target of several federal- and state-wide initiatives by agencies such as Substance Abuse and Mental Health Services Administration (SAMHSA), Centers for Disease Control and Prevention (CDC), Drug Enforcement Administration (DEA), and the White House Office of National Drug Control Policy. Although the FIW for Opioid ADEs acknowledged that there is a continuum of aberrant drug behaviors and that intentional misuse and abuse are strong predictors for prescription opioid ADEs, it was decided that prevention of intentional suicide or nonmedical use of opioids was outside of the scope of the Action Plan. The Action Plan defers to the work of other federal agencies with regard to the specific issue of prescription opioid misuse and abuse.

Nonetheless, the accurate categorization of opioid overdoses as having resulted during the course of therapeutic use or owing to abuse/misuse is extremely challenging from a public health surveillance and epidemiologic perspective. Patients that are appropriately prescribed opioids can gradually drift into the spectrum of misuse/abuse through aberrant drug behaviors, such as increasing the dose or frequency of their opioids without consulting their prescriber [14]. This makes it difficult to target patients that are misusing/abusing opioids because it is challenging to identify patients that drift from therapeutic use to misuse/abuse. The ambiguous definitions of misuse/abuse also make it difficult to draw conclusions from available data. For example, the CDC identified over 16,651 opioid overdose deaths in 2011 [10], but it was not possible to distinguish deaths that occurred in the normal course of care when using medications as prescribed versus deaths as a result of intentional misuse and abuse. Data from the Drug Abuse Warning Network estimates over 420,000 ED visits resulted from non-medical use of prescription pain relievers in 2011 [12]. However, limited data are available about the number of ED visits for opioid ADEs resulting during the normal course of care. Due to these limitations, much of the data cited
Throughout the opioid section of the Action Plan may include patients that deliberately misuse/abuse opioids. This is 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 facilities 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 utility and role of intermediate outcomes is not clearly established in the context of prevention of opioid ADEs. 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 scope of 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 2 provides a summary of opioid ADE-related metrics from currently-available federal surveillance systems.
### Table 11. Summary of Federal and Relevant State Surveillance Systems Specific to Opioid ADEs

<table>
<thead>
<tr>
<th>Source</th>
<th>Overview</th>
</tr>
</thead>
</table>
| National Vital Statistics System (NVSS), CDC                 | - Collects data from all death certificates filed by states and territories in the US, including deaths involving drugs.  
- Uses ICD codes to identify the underlying cause of death (e.g., drug overdose) and contributing causes (e.g., specific pharmaceutical or illicit drugs) |
| Drug Abuse Warning Network (DAWN), SAMHSA                    | - 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 and is now being combined into a larger National Center for Health Statistics (NCHS) survey. |
| Automation of Reports and Consolidation Orders System (ARCOS), DEA | - Collects national data related to certain controlled substance sales/distribution from the manufacturer and/or distributor to the point of sale to the retail level registrant. |
| Prescription Behavior Surveillance System (PBSS), CDC, FDA, BJA (under development) | - Will collect de-identified data from multiple state 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)                | - 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 identification, prescriber information, dispensing pharmacy information, and drug information. |

**Abbreviations:** ADE = adverse drug event; ARCOS = Automation of Reports and Consolidation Order Systems; 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; SAMSHA = Substance Abuse and Mental Health Services Administration
### Table 12. Summary of Opioid ADE-related Metrics Collected by Currently-Available Federal and Relevant State Surveillance Systems

<table>
<thead>
<tr>
<th>Geographic Scope</th>
<th>Data Collection Method</th>
<th>Opioids ADE or Management Metrics: Inpatient Settings</th>
<th>Opioids ADE or Management Metrics: Outpatient Settings</th>
</tr>
</thead>
</table>
| **National ADE Incidence/Rates** | Administrative claims and/or EHR data | **AHRQ (NIS):**  
- HCUP: Inpatient stays with ICD-9 codes | **AHRQ (NEDS):**  
- HCUP: ED visits with ICD codes |
| Medical-record review | **AHRQ:**  
- MPSMS: Opioids are not currently captured by MPSMS system, but will be included after the conversion to QSRS | **CDC:**  
- NEISS-CADES- ED visits for opioid overdose, and other ADEs, not related to misuse/abuse  
- NVSS-Mortality- Deaths due to opioid overdose | **SAMSHA:**  
- DAWN- ED visits for opioid overdose related to misuse/abuse |
| **Process/Exposure Data** | Not available | **DEA:**  
- ARCOS- total number/amount of opioids sold by manufacturers/distributors to retail registrants as an estimate of exposure/supply |  |
| **Regional-/Facility-level ADE Incidence/Rates (Quality Improvement)** | Administrative claims and/or EHR data | Not available | **DOD:**  
- Outpatient clinic visits, ED visits, hospitalizations with ICD-9 codes and/or CPT codes  
- **VA:**  
- ATHENA- Opioid process measures  
- Outpatient clinic visits, ED visits, hospitalizations for opioid overdoses, other relevant ADEs  
- **State:**  
- PDMP- Number of opioids prescribed linked with patient and prescriber  
- PDMP- Number of patients with multiple opioid prescribers  
- PDMP- Number of patients on high-daily dose of opioids |
Table 12. Summary of Opioid ADE-related Metrics Collected by Currently-Available Federal and Relevant State Surveillance Systems (continued)

<table>
<thead>
<tr>
<th>Geographic Scope</th>
<th>Data Collection Method</th>
<th>Opioids ADE or Management Metrics: Inpatient Settings</th>
<th>Opioids ADE or Management Metrics: Outpatient Settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Reports</td>
<td>FDA: ▪ Clinician-diagnosed or patient-reported ADE</td>
<td>FDA: ▪ Clinician-diagnosed or patient-reported ADE</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ADEs = Adverse Drug Events; ARCOS = Automation of Reports and Consolidation Order Systems; CPT = Current Procedural Terminology; DAWN = Drug Abuse Warning Network; DEA = Drug Enforcement Administration; ED = Emergency Department; EHR = Electronic Health Records; PDMP = Prescription Drug Monitoring Program; SAMSHA = Substance Abuse and Mental Health Services Administration

**Metrics that reflect the outcome and process measures related to opioid ADEs are lacking**

Currently, few metrics are designed to assess national- or facility-level burden of opioid ADEs. Opportunities for improvement exist in the development 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.

**Continued support of PDMPs and PBSS represent important opportunities for advancing surveillance to reduce opioid ADEs**

One of the greatest opportunities for advancing surveillance is to continue to develop PDMPs and the PBSS to capture the data needed to identify high-risk prescribing patterns and to better understand risk factors for opioid overdose. Ideally, PDMPs would be able to track patients across settings (including across different states), identify high-risk prescribing practices, and alert prescribers to aberrant behaviors in patients prescribed opioids.
Future surveillance efforts will have to capture opioid ADEs based on validated process and outcome measures, differentiate between opioid ADEs that occur in the normal course of care versus misuse/abuse, and identify ADEs that occur during transitions of care outside of the health care system.

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 the data to allow for accurate, real-time evaluation of trends in opioid outcomes and validated process measures. Figure 18 summarizes the FIW for Opioids’ recommendations to advance surveillance strategies for opioid ADEs.
Figure 18. Federal Interagency Workgroup Recommendations for Actions that Can Potentially Advance Surveillance Strategies for Opioids 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 and assess novel measures for identifying and recording ADEs (outlined in Table 14)
- Address strengths and limitations in using process measures to identify opioid ADEs and measure associations between changes in 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
- Address gaps in standard surveillance definitions for opioid-related overdose events
  - Need for better distinguishing between overdose events that occur as a result of misuse and abuse versus normal course of care
  - Reduce for bias or misclassification in characterizing opioid ADEs based on retrospective medical review
- Address strengths and limitations in using process measures to identify opioid ADEs and measure associations between changes in process measures and risk of opioid ADEs
- Identify appropriate ADE surveillance metrics for opioid ADEs
- Promote increased use of PDMP systems by providers and maintenance of funding for PDMP development at the state and federal level

**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 opioid prescribing for CNCP address the issue of opioid safety [3, 15, 16, 17, 18]. Specifically, the guidelines make patient-centered care central to the decision making process through assessing patients at risk for opioid overdose and balancing the goals of pain management with the risk of opioid overdose. There are different risk factors for inpatient and outpatient opioid ADEs. In inpatient settings, system-wide changes may be the most important target for ADE prevention because many opioid ADEs occur due to 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 (i.e., inappropriate dose, issues of adherence, aberrant drug behavior) are likely to play a much larger role in causing opioid ADEs than in inpatient settings [14]. Federal agencies have a number of strategies to promote safe opioid prescribing and reduce opioid ADE prevention that can serve as a model for private stakeholders. Current and future federal assets are summarized in Figure 19.
### Resources for Safer Care – Health Care Provider Knowledge

- **DOD/VA:**
  - 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 Fort Bragg—primary care clinicians provide high-risk patients prescribed opioids with kits containing naloxone along with training in identifying and responding to overdose symptoms

- **FDA:**
  - Risk Evaluation and Mitigation Strategies (REMs)—created strategy for extended release and long-acting opioids; FDA developed a “Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics,” and maintains a list of compliant Continuing Education (CE) programs that include this provider curriculum
  - Opioid Dose Conversion Table—effort to develop safe and reliable dose conversion table based on updated evidence

- **IHS:**
  - TeleBehavioral Health Center of Excellence Pain and Addictions course—15 series webinar training program providing specialized training on how to treat pain and addictions

- **NIH:**
  - NIDAMED Physician Education Tools— the National Institute on Drug Abuse hosts a website with tools and resources for medical professionals for safe pain management including two classes entitled “Safe Prescribing for Pain” and “Managing Pain Patients Who Abuse Rx Drugs”

### Resources for Patients and Family Engagement

- **ACLS:**
  - Chronic Disease Self-Management Education Programs—provides education and tools to older adults and adults with disabilities with education and tools to help them better manage chronic conditions including chronic pain

- **DEA:**
  - National Take-Back Initiative—program to give 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 long-acting opioids

- **VA:**
  - “Taking Opioids responsibly: For Your Safety and the Safety of Others” patient education tool

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i Available at: [http://www.drugabuse.gov/nidamed/etools](http://www.drugabuse.gov/nidamed/etools)

ii Available at: [http://www.aoa.gov/AoARoot/AoA_Programs/HPW/ARRA/PPHF.aspx](http://www.aoa.gov/AoARoot/AoA_Programs/HPW/ARRA/PPHF.aspx)

iii Available at: [http://www.er-la-opioidrems.com/IwgUI/rems/pcd.action](http://www.er-la-opioidrems.com/IwgUI/rems/pcd.action)
Figure 19. Current and Potential Federal Assets Related to Safe Management of Opioid Therapy as Identified by National Quality Strategy Priorities (continued)

**Resources to Promote Best Practices within Communities**

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

**Resources for Communication and Care Coordination**

- **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 is authorized to prescribe opioids

- **VA:**
  - **Systems to track patient progress**—VA is piloting a mobile application 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 multi-specialty 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.

**Inpatient Settings**

The Joint Commission identified opioids as an important cause of inpatient ADEs, with the most dangerous ADE being respiratory depression. The Joint Commission Sentinel Alert “Safe Use of Opioids in Hospitals” recommends improved assessment and management of pain to avoid accidental opioid overdose [19]. Guidelines recommend a systematic approach to patient assessment and patient monitoring. Federal agencies have identified initiating patients on a high dose of opioids, converting between opioid formulations, and opioid dose titration as potential targets for reducing opioid ADEs. Figure 20 outlines opportunities to advance ADE prevention strategies/tools in inpatient settings organized around the National Quality Strategy priorities.

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1 Available at: [http://www.va.gov/PAINMANAGEMENT/VHA_Pain_Management_Strategy.asp](http://www.va.gov/PAINMANAGEMENT/VHA_Pain_Management_Strategy.asp)
Outpatient Settings

Opioid ADEs in outpatient settings are a multifaceted problem. The outpatient setting is complicated by the added complexity of prescription opioid misuse and abuse that is one of the main drivers of prescription opioid overdoses. Although this Action Plan does not directly address the issue of misuse/abuse, it does advocate for steps to improve prescribing behaviors to prevent patients that are prescribed opioids from engaging in overt substance abuse. While the factors driving opioid overdoses are not completely understood, a number of factors have been associated with increased risk of opioid overdose in the outpatient settings and can serve as targets for outpatient opioid overdose prevention. These risk factors are: high daily opioid dose [20, 21, 22, 23, 24], concomitant use of central nervous system (CNS) depressants (especially benzodiazepines) [14, 20, 25], recent initiation of opioid therapy in naïve patients patients [20, 26, 27], multiple opioid prescribers [14, 28], mental health disorder co-
morbidities [14, 20, 21, 28, 29], medical co-morbidities (e.g., sleep apnea) [3], active or history of substance abuse [20, 21, 28, 29], aberrant drug related behaviors [14, 28, 30, 31], and high-risk formulations (e.g., methadone) [27]. Federal agencies can play an essential role in promoting evidence-based strategies to address opioid overdose risk factors and promote safe practices.

**Figure 21** presents opportunities to advance the ADE prevention strategies/tools in outpatient setting. These prevention opportunities are organized around the National Quality Strategy Priorities.

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

| Safer Care | Expand dissemination of evidence-based opioid guidelines/protocols (e.g., dosing changes, management of high-risk patients) |
|           | Improve availability and uptake of safe opioid prescribing practices |
| Patient and Family Engagement | Develop and distribute patient education materials and strategies using the principles of health literacy |
|                                | Spread public health message promoting safe opioid storage, use, and disposal and not sharing opioids with friends or family |
| Effective Communication and Coordination of Care | Develop more optimal and integrated Health IT opioid management tools |
|                                                | Integrate opioid-specific targets into care transition models |
| Science-driven Prevention and Treatment | Promote “systematic and coordinated care” |
|                                           | 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 practices |
| Promoting Best Practices within Communities | 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 through the increased use of prescribing guidelines for chronic non-cancer pain and appropriate provider training through didactic training, Continuing Education (CE) Credits, and training at key points in clinical training (i.e., licensure).

Opioid prescribing guidelines for the treatment of CNCP promote the assessment of patients for risk factors prior to initiating opioid therapy and recommend continuing assessment of the therapy goals and outcomes to determine the effectiveness and appropriateness of therapy for the patient. Prescribing guidelines also provide consensus-based strategies on how to reduce the risk for opioid overdose. Federal agencies should work to educate clinicians on safe and appropriate opioid prescribing and use available mechanisms to promote clinician education through didactic education, CMEs, and assessments of clinicians’ knowledge of safe opioid prescribing practices.

Federal agencies should promote patient-centered, multimodal, team-based care to personalize pain management, properly manage patients with high-risk medical and mental 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 that identify and properly manage medical 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 non-opioid pharmacological therapies and non-pharmacological therapies as part of an overall pain management plan.

Federal agencies should develop and encourage the use of patient education materials and tools, using health literacy principles, to empower the patient to use opioids safely and encourage patient engagement.

Patients can play a major role to increase the safe use of prescription opioids. To promote safe opioid use at home, patients need to 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.
Federal agencies involved in patient care play an important role in assessing and promoting best practices for pain management and opioid safety

The BOP, DOD, IHS, and VA, all of whom provide direct patient care, have taken steps to advance the practice of pain management and improve opioid safety. Because the DOD and VA serve active and veteran military members who often have injuries requiring pain management, these agencies have been at the cutting edge of evidence-based pain management and systems to promote opioid safety.

Table 13 outlines the initiatives that are currently underway in VA and DOD systems that can be evaluated, modeled, and expanded to the private sector. DOD and VA have developed their own opioid prescribing guidelines for CNCP [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 can still improve and requires a system of continuous improvement to continue to increase adherence to guidelines. 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

<table>
<thead>
<tr>
<th>System</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic Strategy</td>
<td>▪ VA National Pain Management Strategy — outlines systematic strategies to improve pain management while maintaining opioid safety</td>
</tr>
<tr>
<td></td>
<td>▪ 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</td>
</tr>
<tr>
<td>Performance Measurement</td>
<td>▪ 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</td>
</tr>
<tr>
<td></td>
<td>▪ Process measures — VA developed a set of administrative data-based metrics which assess facility-level adherence to key recommendations of the VA/DOD Clinical Practice Guideline for Opioid therapy for Chronic Pain</td>
</tr>
<tr>
<td></td>
<td>▪ Outcome Measures — VA’s electronic Mental Health Assistant makes validated assessments for patient outcomes, such as the Pain Outcomes Questionnaire (POQ), West Haven Yale Multidisciplinary Pain Inventory (WHYMPI), and the Brief Pain Inventory (BPI) available for use in the EHR</td>
</tr>
<tr>
<td>Point of Care Clinical Management and Information Support</td>
<td>▪ VA’s ATHENA System — Opioid system is a point of care decision support system to guide opioid management</td>
</tr>
<tr>
<td></td>
<td>▪ VA inpatient tools for converting between different strengths/formulations of opioids</td>
</tr>
</tbody>
</table>
Table 13. Systematic Actions from VA and DOD Facilities for Safe and Effective Opioid Use for Pain Management (continued)

<table>
<thead>
<tr>
<th>System</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-morbidity Management/</td>
<td>Mental Health Assessment and Treatment—VA requires annual screening for depression using the Patient Health Questionnaire (PHQ-2) and post-traumatic stress disorder (PTSD) using the Primary Care—PTSD (PC-PTSD) screen with referral for additional assessment and treatment of positive cases</td>
</tr>
<tr>
<td>Individualized Care</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** BPI = Brief Pain Inventory; EHR = Electronic Health Record; PHQ-2 = Patient Health Questionnaire; POQ = Pain Outcomes Questionnaire; PC-PTSD = Primary Care Post-Traumatic Stress Disorder Screen; PTSD = Post-Traumatic Stress Disorder; WHYMPI = West Haven Yale Multidisciplinary 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 CY 2013 Final Call Letter on April 2, 2012 and 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 adverse drug events may be reduced.

As part of their opioid overutilization programs, Part D sponsors are expected to use retrospective drug utilization review (DUR) 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 of opioid ADEs is based on cumulative daily morphine equivalent dose (MED) across all opioids used by the beneficiary for chronic
non-cancer pain and accounts for the beneficiary’s use of multiple prescribers and pharmacies. The guidance also addresses data-sharing between Part D plan sponsors when a beneficiary, for whom an individual claim control has been implemented to prevent the 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 late 2013. 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 upon cumulative MED across the opioid class as soon as possible.

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

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 or 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 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 22**. 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

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1 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.
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. While the FIW recommendations address the public payor perspective, the goal is that the opportunities identified will also influence private sector advancements in this area allowing for public payors to learn from successful private sector strategies in this regard.

Figure 22. Federal Interagency Workgroup Recommendations for Actions that Can Potentially Advance Policy Strategies for Opioid ADE Prevention

**Actions that Can Potentially Advance Health Policy Strategies for Preventing Opioid ADEs**

**Inpatient Settings**
- Expand national health care quality reporting measures to include concepts related to multi-disciplinary, 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**
- Expand national health care quality reporting measures to include ones specific to opioid ADE prevention through process measures that identify high-risk practices
- Address payment/coverage barriers to uptake of evidence-based, high-quality ADE prevention strategies and multimodal, team-based pain management
- 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 opioid therapy and pain management

**Abbreviations:** ADE= Adverse Drug Event; PDMP= Prescription Drug Management Program
Health Information Technology (HIT)

Federal agencies that develop, promote, and incentivize EHR standards play an important role in advancing HIT-based strategies for inpatient opioid ADE prevention

EHRs can serve an important role in providing patient specific information that is necessary to make appropriate clinical decisions by providers. EHRs can also provide support the use of Clinical Decision Support (CDS) to identify appropriate starting doses and morphine equivalent doses (MED) between different opioid formulations to allow clinicians to safely transition between opioid formulations and identify high doses.

EHR (Stage 3) Meaningful Use requirements that can potentially advance opioid ADE prevention have been recently proposed by the Federal Interagency Workgroup (FIW) for ADEs

Health care quality measures are important in helping to advance ADE prevention efforts. In June 2013, the FIW for Opioid ADEs presented recommendations to the HHS Office of the National Coordinator (ONC) for consideration in Stage 3 of the Meaningful Use Incentive Program. These recommendations can potentially support opioid ADE prevention and monitoring and are summarized in Table 14. Unfortunately, there are currently no nationally endorsed metrics for opioid ADEs. As a result, the proposed recommendations were developed de novo or based on VA specific measures and require further development and validation as a tool for reducing opioid ADEs.

The outpatient metrics detailed in Table 14 are targeted towards long-term opioid use for CNCP and are modeled after measures that are currently in use by the VA to measure adherence to the VA/DOD Clinical Practice Guidelines for the Management of Opioid Therapy for Chronic Pain. The inpatient measures, which are also detailed in Table 14, are based on measures for appropriate monitoring that are currently under development by CMS.
Table 14. EHR (Stage 3) Meaningful Use Requirements that Can Potentially Advance Opioid ADE Prevention as Proposed by the Federal Interagency Workgroup (FIW) for ADEs

<table>
<thead>
<tr>
<th>Metric</th>
<th>Description/Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient Clinical Quality Measure Concepts</strong></td>
<td></td>
</tr>
<tr>
<td>Patients on high daily dose of long-term opioid therapy</td>
<td>▪ There is an increased risk of opioid ADEs with high daily dose of opioids</td>
</tr>
<tr>
<td>Patients co-prescribed long-term opioid therapy and CNS depressants</td>
<td>▪ Co-prescribing of opioids with CNS depressants, especially benzodiazepines, is associated with opioid overdose deaths</td>
</tr>
<tr>
<td>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</td>
<td>▪ All guidelines recommend assessment of risk related to substance abuse prior to initiating opioids and while patients are on therapy</td>
</tr>
<tr>
<td>Patients on long-term opioid therapy that were checked in the relevant Prescription Drug Monitoring Program prior to initiating therapy and at least every year if on chronic opioid therapy</td>
<td>▪ Guidelines recommend monitoring PDMPs when available ▪ Early data shows that PDMPs may be effective, though more research will be necessary as PDMPs continue to be developed and used</td>
</tr>
<tr>
<td>Patients on long-term opioid therapy that have evidence of a written opioid care management plan</td>
<td>▪ All guidelines recommend that all 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</td>
</tr>
<tr>
<td>Number of patients on long-term opioid therapy that have evidence of mental health assessment</td>
<td>▪ All guidelines recommend assessment for mental health disorders prior to initiating opioids, and treatment as appropriate</td>
</tr>
<tr>
<td>Number of patients in facility or practice prescribed opioids</td>
<td>▪ Based on a VA measure that is used to compare prescribing rates across facilities</td>
</tr>
<tr>
<td><strong>Inpatient Clinical Quality Measure Concepts</strong></td>
<td></td>
</tr>
<tr>
<td>Proper monitoring of patients on IV patient controlled analgesia (PCA) opioid therapy</td>
<td>▪ Guidelines recommend appropriate monitoring as a strategy to reduce PCA-related respiratory depression</td>
</tr>
<tr>
<td>Opioid-naïve patients started on high dose opioids in the inpatient setting</td>
<td>▪ Prescribing errors are a significant problem that can lead to opioid overdose in the inpatient setting, especially in high potency formulations</td>
</tr>
</tbody>
</table>
Table 14. EHR (Stage 3) Meaningful Use Requirements that Can Potentially Advance Opioid ADE Prevention as Proposed by the Federal Interagency Workgroup (FIW) for ADEs (continued)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Description/Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Decision Support (CDS) Rule Concepts</td>
<td></td>
</tr>
<tr>
<td>Clinical Decision Support Rules to support all measures concepts</td>
<td>▪ There should be supporting clinical decision support to promote best practices and improve measured processes</td>
</tr>
</tbody>
</table>

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 and 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 23.
Figure 23. 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, public-private sector collaborations)*

- Evaluate the effectiveness of evidence-based 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
- Study real-world management of patients identified as high-risk for opioid ADEs (e.g., through the establishment of patient registries)
- Evaluate the clinical outcomes of using PDMPs and the effects of 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
- Determine the safety and efficacy of long-term opioid therapy for CNCP
- Examine emerging pharmacogenomics related to hypermetabolizers of opioids
- Pursue innovative drug development for abuse resistant opioids and non-opioid drugs for refractory pain
- Adopt adjunctive and behavioral modalities to augment and reduce opioid use for chronic pain

**Abbreviations:**  
ADE= Adverse Drug Event; CNCP= Chronic Non-cancer Pain; PDMP= Prescription Drug Monitoring Program; UDS= Urine Drug Screen
References


4. Paulozzi, Jones, Mack. CDC *MMWR* November 2011


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 ADE Prevention has facilitated communication and collaborations across 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, as well as identified challenges and opportunities in advancing the field of ADE prevention.

The 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 follow-up to the Action Plan, it will be critical that federal partners initiate collaborations with other public and private stakeholders as well. It is hoped that increased federal attention to the high prevalence and of ADEs and their negative impact on patients, providers, and health care costs will improve awareness and support of these efforts across public and private sectors. Broadly, the 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.
Conclusions and Next Steps

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

Additionally, more coordinated and focused use of health information technology will have a critical role in advancing ADE prevention efforts through various mechanisms including, but not limited to, improvements in detection and monitoring of ADEs based on 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, as well as, integration of clinical decision support tools and health care quality measures targeted specifically at high-priority ADEs.

The success of the Action Plan will depend upon ongoing coordination and collaboration across the federal government and among government agencies, national experts, and key public and private stakeholders. This 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 Action Plan. If the national burden of ADEs is to be reduced, federal partners must continue in their coordinated and aligned efforts towards 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 towards reduction in ADEs from the initial targets of the Action Plan (i.e., anticoagulants, diabetes agents, opioids), efforts will need to be re-tooled to additional and newly-emerging medication safety targets.

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

• Facilitating and coordinating nationwide and state-based efforts to align and enhance ADE surveillance and prevention,

• Coordinating ongoing meetings of the Federal Interagency Steering Committee for ADEs on a quarterly basis to share current federal efforts related to ADE prevention,

• Investigating opportunities to host a public meeting focused on sharing and dissemination of current and future best practices, policies, and research around ADE surveillance and prevention,
Conclusions and Next Steps

- Leverage a cross-cutting federal communication workgroup to conduct outreach and education to public and private stakeholders around ADEs,
- Support continued investment in research to inform and advance medication safety, and
- Identify opportunities to incorporate measures related to high-priority ADE targets into existing and future CMS programs.

Leveraging the extensive experience of HHS and other federal partners in improving the health and welfare of Americans, we are confident the goals outlined in the National Action Plan for ADE Prevention will help advance overall patient safety and wellness across the nation.
# Key Partnerships in Development of the National 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

<table>
<thead>
<tr>
<th>HHS Operating Division/ Federal Agency</th>
<th>Role/Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bureau of Prisons</td>
<td></td>
</tr>
<tr>
<td>BOP</td>
<td>- Provides medical, dental, and mental health to federal inmates in Bureau facilities, including health care delivery, infectious disease management, and medical designations.</td>
</tr>
<tr>
<td>Department of Defense</td>
<td></td>
</tr>
<tr>
<td>DOD</td>
<td>- Ensures health care to active duty members, retired service members, National Guard/Reserve members, families, survivors and others entitled to DOD medical care.</td>
</tr>
<tr>
<td>Department of Health &amp; Human Services</td>
<td></td>
</tr>
</tbody>
</table>
| AHRQ                                   | - Supports research to identify root causes of threats to patient safety, inform decisions and improves the quality of health care services.  
                                         - Manages systems to collect patient safety data. |
| ACL                                    | - Provides resources/programs to support care coordination and consumer and caregiver activation |
| CDC                                    | - 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                                    | - 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)

<table>
<thead>
<tr>
<th>HHS Operating Division/Federal Agency</th>
<th>Role/Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Department of Health &amp; Human Services (continued)</td>
<td>Involved in risk mitigation</td>
</tr>
<tr>
<td></td>
<td>Supports ADE surveillance</td>
</tr>
<tr>
<td>FDA</td>
<td>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.</td>
</tr>
<tr>
<td>HRSA</td>
<td>Ensures that comprehensive, culturally acceptable personal and public health services are available and accessible to American Indian and Alaska Native people.</td>
</tr>
<tr>
<td>IHS</td>
<td>Conducts and supports research in 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.</td>
</tr>
<tr>
<td>NIH</td>
<td>Advises on policy development, and is responsible for major activities in policy coordination, legislation development, strategic planning, policy research, evaluation, and economic analysis.</td>
</tr>
<tr>
<td>OS/ASPE</td>
<td>Supports the adoption of health information technology and the promotion of nationwide health information exchange to improve health care.</td>
</tr>
<tr>
<td>VA</td>
<td>Provides health care to eligible Veterans, partners with other federal departments and agencies to measure the frequency and impact of ADEs.</td>
</tr>
<tr>
<td></td>
<td>Supports surveillance</td>
</tr>
</tbody>
</table>

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 and Medicaid Services; DOD = Department of Defense; FDA = Food and Drug Administration; HRSA = Health Resources and Services Administration; IHS = Indian Health Services; NIH = National Institute for Health; ONC = Office of the National Coordinator for Health IT; OS = Office of the Secretary; VA = U.S. Department of Veterans Affairs
## Overview of Federal Systems that Conduct ADE Surveillance

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

<table>
<thead>
<tr>
<th>Agency</th>
<th>AHRQ</th>
<th>AHRQ</th>
<th>AHRQ</th>
<th>CDC</th>
<th>FDA</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>System Name</td>
<td>HCUP-Nationwide Inpatient Sample (NIS); State Inpatient Databases (SID)</td>
<td>HCUP-NEDS</td>
<td>MPSMS*</td>
<td>NEISS-CADES</td>
<td>FAERS</td>
<td>Sentinel Initiative Mini-Sentinel Pilot</td>
</tr>
<tr>
<td>Active or Passive?</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Passive (voluntary)</td>
<td>Active</td>
</tr>
<tr>
<td>System Focus</td>
<td>Research and statistical reporting on utilization and costs of care provided in U.S. hospitals</td>
<td>Research and statistical reporting on utilization and costs of care provided in U.S. emergency departments</td>
<td>Hospital complications from select medications (e.g., anticoagulants, insulin, digoxin)</td>
<td>Monitoring acute harms from commonly-used medications in ambulatory care</td>
<td>Signal detection and assessment</td>
<td>Signal assessment</td>
</tr>
</tbody>
</table>
Table B–1. Federal Systems for Conducting ADE Surveillance—National Surveillance Systems (continued)

<table>
<thead>
<tr>
<th>Agency</th>
<th>AHRQ</th>
<th>AHRQ</th>
<th>AHRQ</th>
<th>CDC</th>
<th>FDA</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting of Drug Exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient or outpatient (can distinguish between exposure setting when the data system provides information on whether diagnoses were present on admission [POA] or not -- this information is available for a subset of states contributing to HCUP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department (no POA information is provided for ED visits)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Select adult inpatient populations (those with hospital discharge diagnosis of HF, AMI, or pneumonia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient (all ages)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All settings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Inpatient (incl., procedures)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Outpatient (incl., procedures)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Geographic Scope |
| ▪ NIS: National (~1000 hospitals) |
| ▪ SID: State |
| ▪ National (~1000 hospitals) |
| ▪ Regional stratification |
| ▪ National (~800 of ~3400 hospitals) |
| ▪ No regional stratification |
| ▪ National (~63 hospitals) |
| ▪ No regional stratification |
| Foreign and domestic |
| Varies with data partners/sources. Currently Sentinel covers > 125 million lives which do not constitute a nationally representative sample. |

| Data Source(s) |
| Hospital billing data |
| ED billing data |
| Hospital discharge medical records |
| ED medical records |
| ▪ (Primarily) Post-marketing, spontaneous AE reports |
| ▪ (Some) Clinical trial AE reports |
| ▪ Insurance claims |
| ▪ Public and private administrative claims |
Table B–1. Federal Systems for Conducting ADE Surveillance—National Surveillance Systems (continued)

<table>
<thead>
<tr>
<th>Agency</th>
<th>Data Collection Method</th>
<th>Case Identification Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHRQ</td>
<td>NIS is a stratified sample of about 1,000 hospitals; all discharge records (~8 million) are retained in the dataset</td>
<td>Algorithmic detection using ICD-9-CM codes</td>
</tr>
<tr>
<td>AHRQ</td>
<td>SID are based on discharge data collected by statewide data organizations and shared with AHRQ through voluntary agreements</td>
<td>Algorithmic detection based on chart abstraction of select ADEs (select anticoagulants, antibiotic-related CDI, insulin, oral diabetes agents, digoxin)</td>
</tr>
<tr>
<td>AHRQ</td>
<td>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.</td>
<td>Algorithmic detection based on chart abstraction using clinician diagnosis as it appears in medical record narrative (not ICD-9 coding)</td>
</tr>
<tr>
<td>CDC</td>
<td>Random national sample</td>
<td>MedDRA Preferred Terms (PTs) or Standardized MedDRA Queries (SMQs)</td>
</tr>
<tr>
<td>FDA</td>
<td>National stratified probability sample</td>
<td>Algorithm detection using drug exposure codes (dispensing), ICD-9 codes (diagnosis), and CPT (procedure) codes</td>
</tr>
<tr>
<td>FDA</td>
<td>Voluntarily-submitted reports</td>
<td>Database queries</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>Agency</th>
<th>BOP</th>
<th>DOD</th>
<th>DOD</th>
<th>IHS</th>
<th>VHA</th>
<th>VHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>System Name</td>
<td>N/A</td>
<td>Pharmacovigilance</td>
<td>Patient Safety</td>
<td>Resource and Patient Management</td>
<td>VA ADERs</td>
<td>Department of VA Integrated Databases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Defense Application System</td>
<td>Reporting System</td>
<td>System (RPMS-EHR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active or Passive?</td>
<td>Passive (voluntary)</td>
<td>Active</td>
<td>Passive (voluntary)</td>
<td>Passive (voluntary)</td>
<td>Active</td>
<td></td>
</tr>
<tr>
<td>Surveillance Population</td>
<td>Inmates in facilities under the supervision of Bureau of Prisons</td>
<td>DOD (active duty, family members and retirees and family members)</td>
<td>DOD (active duty, family members and retirees and family members)</td>
<td>Federally recognized American Indians and Alaska Natives</td>
<td>VHA</td>
<td>VHA</td>
</tr>
<tr>
<td>System Focus</td>
<td>Quality improvement</td>
<td>Quality improvement</td>
<td>Quality improvement</td>
<td>Quality improvement</td>
<td>Quality improvement</td>
<td></td>
</tr>
<tr>
<td>Setting of Drug Exposure</td>
<td>Inpatient</td>
<td>Inpatient (all ages)</td>
<td>Inpatient (military treatment facilities)</td>
<td>Inpatient</td>
<td>Inpatient (VHA facilities)</td>
<td>Inpatient</td>
</tr>
<tr>
<td></td>
<td>Outpatient</td>
<td>Outpatient (all ages)</td>
<td>Outpatient (military treatment facilities)</td>
<td>Outpatient</td>
<td>Outpatient (VHA facilities)</td>
<td></td>
</tr>
<tr>
<td>Geographic Scope</td>
<td>Regional BOP</td>
<td>National DOD</td>
<td>National DOD-run facilities</td>
<td>National HIS</td>
<td>National VHA</td>
<td>National VHA</td>
</tr>
<tr>
<td></td>
<td>Facility</td>
<td>Facility</td>
<td>Facility</td>
<td>Regional area office</td>
<td>Regional VHA</td>
<td>Regional VHA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Service</td>
<td>Facility-level</td>
<td>Facility</td>
<td>VHA network</td>
<td>VHA network</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Service-level</td>
<td>Individual patient care</td>
<td>Facility</td>
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<td></td>
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<td></td>
<td>Facility</td>
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</tr>
</tbody>
</table>
Table B–2. Federal Systems for Conducting ADE Surveillance—Federal Health Systems (continued)

<table>
<thead>
<tr>
<th>Agency</th>
<th>BOP</th>
<th>DOD</th>
<th>DOD</th>
<th>IHS</th>
<th>VHA</th>
<th>VHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Source(s)</td>
<td>Spontaneous AE Reports</td>
<td>BOP EHRs</td>
<td>DOD EHRs</td>
<td>Patient Safety Reporting System Submitted Reports</td>
<td>IHS</td>
<td>VHA EHRs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DOD administrative claims</td>
<td>Patient Safety Reporting System Submitted Reports</td>
<td></td>
<td>VHA EHRs</td>
<td>VHA administrative claims</td>
</tr>
<tr>
<td>Data Collection Method</td>
<td>EHR Review</td>
<td>Database queries (automated and ad hoc; updated quarterly)</td>
<td>Electronically-submitted reports</td>
<td>Database queries</td>
<td>Database queries</td>
<td>Database queries</td>
</tr>
<tr>
<td>Case Identification Method</td>
<td>Review of cases with prescribed medication (anticoagulants)</td>
<td>Algorithmic detection using combination of drug exposure/J-code and ICD-9/CPT, LOINC codes</td>
<td>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</td>
<td>Algorithmic detection using ICD-9 codes</td>
<td>MedDRA codes</td>
<td>Algorithmic detection using ICD-9 codes</td>
</tr>
</tbody>
</table>

* Adverse Drug Reaction (ADR): a sub-type 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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADE</td>
<td>Adverse drug event</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>AHRQ</td>
<td>Agency for Healthcare Research &amp; Quality</td>
</tr>
<tr>
<td>BOP</td>
<td>Bureau of Prisons</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CDI</td>
<td>Clostridium difficile infection</td>
</tr>
<tr>
<td>CPT</td>
<td>Current Procedural Terminology</td>
</tr>
<tr>
<td>DOD</td>
<td>Department of Defense</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency department</td>
</tr>
<tr>
<td>EHR</td>
<td>Electronic Health Record</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FAERS</td>
<td>FDA Adverse Event Reporting System</td>
</tr>
<tr>
<td>HCUP-NEDS</td>
<td>Healthcare Cost and Utilization Project – Nationwide Emergency Department Sample</td>
</tr>
<tr>
<td>HCUP-NIS</td>
<td>Healthcare Cost and Utilization Project – Nationwide Inpatient Sample</td>
</tr>
<tr>
<td>HF</td>
<td>Heart failure</td>
</tr>
<tr>
<td>ICD-9</td>
<td>International Classification of Diseases (ICD), Version 9</td>
</tr>
<tr>
<td>IHS</td>
<td>Indian Health Service</td>
</tr>
<tr>
<td>LOINC</td>
<td>Logical Observation Identifiers Names and Codes</td>
</tr>
<tr>
<td>MPSMS</td>
<td>Medicare Patient Safety Monitoring System</td>
</tr>
<tr>
<td>NEISS-CADES</td>
<td>National Electronic Injury Surveillance System – Cooperative Adverse Drug Events Surveillance System</td>
</tr>
<tr>
<td>POA</td>
<td>Present on admission</td>
</tr>
<tr>
<td>PTs</td>
<td>MedDRA Preferred Terms</td>
</tr>
<tr>
<td>RPMS</td>
<td>Resource and Patient Management System</td>
</tr>
<tr>
<td>SMQs</td>
<td>Standardized MedDRA Queries</td>
</tr>
<tr>
<td>VA ADERs</td>
<td>VA Adverse Drug Event Database</td>
</tr>
<tr>
<td>VHA</td>
<td>Veterans Health Administration</td>
</tr>
</tbody>
</table>
### 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**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-centered medical home (PCMH)</td>
<td>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 their 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. 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. Source: Davis K et al. (2011). How the Affordable Care Act Will Strengthen the Nation’s Primary Care Foundation. J Gen Intern Med, 26(10): 1201–1203.</td>
</tr>
<tr>
<td>Accountable Care Organization (ACO)</td>
<td>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 where the patient and providers are true partners in care decisions. The Affordable Care Act specifies that an ACO may include the following types of groups of providers and suppliers of Medicare-covered services: • ACO professionals (i.e., physicians and hospitals meeting the statutory definition) in group practice arrangements, • Networks of individual practices of ACO professionals, • Partnerships or joint ventures arrangements between hospitals and ACO professionals, or • Hospitals employing ACO professionals, and • Other Medicare providers and suppliers as determined by the Secretary. Source: <a href="http://www.healthcare.gov/news/factsheets/2011/03/accountablecare03312011a.html">http://www.healthcare.gov/news/factsheets/2011/03/accountablecare03312011a.html</a></td>
</tr>
</tbody>
</table>
## Table C–1. Affordable Care Act Health Care Delivery Models Relevant to ADE Prevention (continued)

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Team-based health care</td>
<td>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.</td>
<td><a href="https://www.nationalahec.org/pdfs/VSRT-Team-Based-Care-Principles-Values.pdf">https://www.nationalahec.org/pdfs/VSRT-Team-Based-Care-Principles-Values.pdf</a></td>
</tr>
</tbody>
</table>
## Overview of CMS Programs/Initiatives with Potential to Advance ADE Prevention

<table>
<thead>
<tr>
<th>Program/Initiative</th>
<th>Description</th>
<th>General ADEs Addressed</th>
<th>ADE Targets Specifically Addressed?</th>
<th>Opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regulatory Oversight</strong></td>
<td></td>
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</tbody>
</table>
| Conditions of Participation (CoPs), Conditions for Coverage (CfCs), and long-term care facility (LTCF) requirements | ▪ Federal health and safety requirements for hospitals and other providers and suppliers  
▪ All Medicare- and Medicaid-participating providers must be in compliance |                                                                                       |                                    |                                                   |
| Hospital CoPs                                          | ▪ 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 |                                                                                       |                                    |                                                   |
| Critical Access Hospital CoPs                         | ▪ Report adverse drug and drug administration errors  
▪ CAHs establish own definition of ADEs |                                                                                       |                                    |                                                   |
| Long Term Care CoPs                                    | ▪ Free of medication errors >5%  
▪ Free of ALL significant medication errors  
▪ Drug regimens not include unnecessary drugs |                                                                                       |                                    |                                                   |
| Home Health Agency CoPs                                 | ▪ Drug regimen review  
▪ Focus on adverse effects, drug interactions, duplicate drugs, noncompliance |                                                                                       |                                    |                                                   |
| **Long Term Care:**                                    | ▪ Specific use/guidelines for  
▪ Anticoagulants  
▪ Diabetes agents  
▪ Opioids |                                                                                       |                                    | Opportunity for advancing ADE prevention          |

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### Table D–1. Overview of CMS Programs and Initiatives that Support the Prevention of ADEs (continued)

<table>
<thead>
<tr>
<th>Program/Initiative</th>
<th>Description</th>
<th>General ADEs Addressed</th>
<th>ADE Targets Specifically Addressed?</th>
<th>Opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regulatory Oversight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survey &amp; Certification</td>
<td>▪ Assess compliance with CoPs and CfCs</td>
<td>▪ Guidelines and policy memos related to prevention of ADEs</td>
<td>No</td>
<td>Opportunity for targeted ADE prevention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Recommendations to follow guidelines of national organizations (e.g. National Coordinating Council for Medication Error Reporting and Prevention)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Value-based Purchasing Financial Incentives</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hospital Inpatient Quality Reporting Program</td>
<td>▪ Hospitals required to report quality measures or subject to payment reduction</td>
<td>No</td>
<td>No</td>
<td>Opportunity for incorporating ADE specific measures</td>
</tr>
</tbody>
</table>
### Table D–1. Overview of CMS Programs and Initiatives that Support the Prevention of ADEs (continued)

<table>
<thead>
<tr>
<th>Program/Initiative</th>
<th>Description</th>
<th>General ADEs Addressed</th>
<th>ADE Targets Specifically Addressed?</th>
<th>Opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Value-based Purchasing</strong>&lt;br&gt;Financial Incentives</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician Quality Reporting System</td>
<td>▪ Eligible professionals receive incentive payment for meeting satisfactory reporting criteria for quality measures&lt;br&gt;▪ Beginning 2015, eligible professionals who do not meet satisfactory reporting criteria of quality measures will be subject to payment reduction&lt;br&gt;▪ Measures publicly reported on CMS website</td>
<td>No</td>
<td>No</td>
<td>Opportunity for incorporating ADE specific measures</td>
</tr>
<tr>
<td>Hospital Based Value Purchasing</td>
<td>▪ Increased payment for hospitals demonstrated high quality&lt;br&gt;▪ Penalties for hospitals demonstrating poor quality</td>
<td>No</td>
<td>No</td>
<td>Opportunity to include ADE measures in future years</td>
</tr>
</tbody>
</table>
Table D–1. Overview of CMS Programs and Initiatives that Support the Prevention of ADEs (continued)

<table>
<thead>
<tr>
<th>Program/Initiative</th>
<th>Description</th>
<th>General ADEs Addressed</th>
<th>ADE Targets Specifically Addressed?</th>
<th>Opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Value-based Purchasing Financial Incentives</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Medicare and Medicaid Electronic Health Record (EHR) Incentive Programs</td>
<td>▪ Incentive payments for hospitals and eligible providers demonstrating effective use of an EHR</td>
<td>▪ Providers must maintain active medication list, implement drug-drug and drug-allergy interaction checks, and implement clinical decision support rules</td>
<td>▪ Specific clinical quality measures related to ADEs:</td>
<td>Opportunity for incorporating additional ADE specific measures, clinical decision support, and EHR functionalities to support ADE prevention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Use of high risk meds in older adults</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Use of aspirin or other antithrombotic</td>
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<td></td>
<td></td>
<td></td>
<td>- ACE inhibitor or ARB therapy</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Beta-blocker</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Pain intensity quantified</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Warfarin time in therapeutic range</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Anticoagulation overlap therapy</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>- Unfractionated Heparin for VTE patients</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>- VTE discharge instructions</td>
<td></td>
</tr>
<tr>
<td><strong>Physician Feedback Program and Value-Based Payment Modifier</strong></td>
<td>▪ Produce annual physician feedback reports</td>
<td>No</td>
<td>No</td>
<td>Opportunities for including ADE specific measures</td>
</tr>
</tbody>
</table>
### Table D–1. Overview of CMS Programs and Initiatives that Support the Prevention of ADEs (continued)

<table>
<thead>
<tr>
<th>Program/Initiative</th>
<th>Description</th>
<th>General ADEs Addressed</th>
<th>ADE Targets Specifically Addressed?</th>
<th>Opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Value-based Purchasing Financial Incentives</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Health Care Innovation Awards</td>
<td>- Supports organizations using new ideas to enhance quality and reduce cost to Medicare, Medicaid, CHIP recipients</td>
<td>- 47 projects provide medication reconciliation or management services</td>
<td>No</td>
<td>Opportunities to address ADEs in future rounds of funding</td>
</tr>
<tr>
<td>Pioneer Accountable Care Organizations (ACOs)</td>
<td>- Shared savings payment model focusing on population based health</td>
<td>- Many of ACOs have participated in efforts to enhance drug safety including use of barcoding, CPOE, medicine decision support, public reporting</td>
<td>No</td>
<td>Opportunities to enhance Pioneer ACO efforts to reduce ADEs</td>
</tr>
<tr>
<td>Multi-Payer Advanced Primary Care Practice</td>
<td>- State level multi-payer reforms to expand advanced primary care practices</td>
<td>- 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</td>
<td>No</td>
<td>Opportunities to expand ADE efforts into additional States</td>
</tr>
<tr>
<td>Community-base Care Transitions Program</td>
<td>- Models to improve care transitions</td>
<td>- All sites provide medication reconciliation</td>
<td>No</td>
<td>Opportunities to enhance focus on ADEs</td>
</tr>
<tr>
<td></td>
<td>- Goals: reduce readmissions, improve quality, cost savings</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Table D–1. Overview of CMS Programs and Initiatives that Support the Prevention of ADEs (continued)

<table>
<thead>
<tr>
<th>Program/Initiative</th>
<th>Description</th>
<th>General ADEs Addressed</th>
<th>ADE Targets Specifically Addressed?</th>
<th>Opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transparency and Associated Incentives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital Compare</td>
<td>▪ Consumer-oriented website providing information on hospital quality</td>
<td>▪ Some hospitals voluntarily report data on ADEs</td>
<td>No</td>
<td>Opportunities to include measures related to ADEs</td>
</tr>
<tr>
<td>Physician Compare</td>
<td>▪ Consumer-oriented website providing information on physician quality and patient experience</td>
<td>No</td>
<td>No</td>
<td>Opportunities to include measures related to ADEs</td>
</tr>
<tr>
<td><strong>Related Initiatives Addressing ADEs</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Initiative to Reduce Avoidable Hospitalizations Among Nursing Facility Residents</td>
<td>▪ Interventions to enhance care coordination for long stay nursing facility residents</td>
<td>▪ Coordinating management of prescription drugs to reduce risk of ADEs</td>
<td>No</td>
<td>Opportunity to expand focus to include specific drug classes</td>
</tr>
</tbody>
</table>
Table D–1. Overview of CMS Programs and Initiatives that Support the Prevention of ADEs (continued)

<table>
<thead>
<tr>
<th>Program/Initiative</th>
<th>Description</th>
<th>General ADEs Addressed</th>
<th>ADE Targets Specifically Addressed?</th>
<th>Opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related Initiatives Addressing ADEs</td>
<td></td>
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</tr>
</tbody>
</table>
| Quality Improvement Organizations | ▪ Network of organizations focused on improving quality of care | ▪ Patient Safety and Clinical Pharmacy Services Collaborative focuses on improve quality and safety among high risk patients, increasing medication therapy management, detection of pADEs and ADEs and reporting on ADEs. | ▪ Reporting on:  
  - The rate of Adverse Drug Events  
  - The potential Adverse Drug Events  
  - Number of beneficiaries on Warfarin with INR in controlled range  
  - Rate of beneficiaries on Warfarin that have INR monitored monthly  
  - Rate of beneficiaries with HgA1c >9%  
  - Rate of beneficiaries inappropriately prescribed an antipsychotic medication | |
| Prevention of Opioid ADEs in Part D | ▪ Part D sponsors must conduct retrospective drug utilization review to identify at risk beneficiaries | ▪ Part D sponsors must engage in case management for at risk beneficiaries | ▪ Appropriate controls on use of opioids including safety edits and quantity limits | Opportunities to expand to additional drug classes |
### Table D–1. Overview of CMS Programs and Initiatives that Support the Prevention of ADEs (continued)

<table>
<thead>
<tr>
<th>Program/Initiative</th>
<th>Description</th>
<th>General ADEs Addressed</th>
<th>ADE Targets Specifically Addressed?</th>
<th>Opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related Initiatives Addressing ADEs</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Regional Chief Medical Officers</td>
<td>▪ Serve as CMS liaison with medical community</td>
<td>▪ Provide education on identification and reduction of ADEs</td>
<td>▪ Importance of controlled blood pressure &amp; management of diabetes; appropriate use of antipsychotics in nursing home; and medication reconciliation</td>
<td>Opportunities to incorporate key information from action plan into presentations and educational outreach</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Participate in intra-agency programs including Prescription Drug Monitoring Program</td>
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<tr>
<td></td>
<td></td>
<td>▪ Present on importance of reducing ADEs across region</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Working on appropriate use of antipsychotics in nursing homes</td>
<td></td>
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</tbody>
</table>
Table D–1. Overview of CMS Programs and Initiatives that Support the Prevention of ADEs (continued)

<table>
<thead>
<tr>
<th>Program/Initiative</th>
<th>Description</th>
<th>General ADEs Addressed</th>
<th>ADE Targets Specifically Addressed?</th>
<th>Opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Related Initiatives Addressing ADEs</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>National Coverage Determination</td>
<td>▪ Determines coverage policies for Medicare services and equipment</td>
<td>▪ Two determinations directly relate to prevention of ADEs</td>
<td>▪ Medicare coverage for home prothrombin time testing to help patients on Warfarin who may be out of therapeutic range</td>
<td>Opportunities to expand coverage determinations to further target reduction in ADEs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>▪ Pharmacogenomic testing to inform physicians of gene variations that might increase or decrease patient’s reaction to Warfarin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>▪ Coverage for home blood glucose monitoring</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>▪ Coverage for testing blood glucose levels in pharmacy</td>
<td></td>
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</tr>
<tr>
<td>State Medicaid Drug Monitoring</td>
<td>▪ State Medicaid agencies use electronic monitoring system to screen prescription drug claims</td>
<td>▪ Drug utilization review looks for duplication, contraindications, incorrect dosage or duration</td>
<td>▪ Depends on State</td>
<td>Opportunity to reach out to states to focus on ADEs related to specific drug classes</td>
</tr>
</tbody>
</table>

**National Action Plan for Adverse Drug Event Prevention**