SECTION

6

Diabetes Agents

Magnitude of the Problem

According to the CDC, diabetes mellitus affects 25.8 million people or 8.3 percent of the U.S. population [1]. In 2010, the national prevalence of diagnosed and undiagnosed diabetes mellitus among persons 20 years of age and older was estimated to be about 258 million persons, or 11 percent of all persons in this age range. For those 65 years of age or older, the prevalence of diagnosed and undiagnosed diabetes was estimated to be 10.9 million persons, or 27 percent of all persons in this age group. Among the 26 million individuals living with diabetes, it is estimated that 95 percent have type 2 diabetes. Patients with type 2 diabetes are at increased risk for serious long-term complications, such as cardiovascular disease and kidney disease [1]. Insulin and oral diabetes agents play an important role in controlling glycemic levels in patients with diabetes mellitus, thereby helping to prevent these complications. Among adults diagnosed with either type 1 or type 2 diabetes, 18 percent take insulin only, 13 percent take both insulin and oral medication, 50 percent take oral medication only, and 18 percent do not take either insulin or oral medication [1].

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

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

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

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

Inpatient Settings

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

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

Outpatient Settings

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

Long-Term Care (LTC) Settings

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

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

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

Surveillance

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

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

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

Geographic Scope	Data Collection Methods	Diabetes Agent ADE or Management Metrics: Inpatient Setting	Diabetes Agent ADE or Management Metrics: Outpatient Setting
National ADE Incidence	Administrative claims and/or EHR data	***AHRQ (HCUP):**** ▪ Inpatient stays with ICD-9-CM (962.3) codes and E-codes (E932.3)	***FDA (Sentinel Initiative, Mini-Sentinel): ***** ▪ ED visits, hospitalizations for hypoglycemic events
National ADE Incidence (+/-Rates)	Medical record review	***AHRQ (MPSMS): ****** ▪ Inpatient stays with combination of laboratory triggers (e.g., glucose ≤50 mg/dL or glucose ≤70 mg/dL but >50 mg/dL) and clinical triggers (e.g., administrations of D50)	***CDC (NEISS-CADES):*** ▪ ED visits, emergent hospitalizations for laboratory abnormalities, hypoglycemic events as diagnosed by clinicians, and documented in medical record narrative
National ADE Incidence	Administrative data and survey data	▪ ***Not available***	***AHRQ (NEDS):*** ▪ Derived from AHRQ's State ED databases and from State inpatient database ▪ Used to estimate number of events (i.e., numerator data)

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

Geographic Scope	Data Collection Methods	Diabetes Agent ADE or Management Metrics: Inpatient Setting	Diabetes Agent ADE or Management Metrics: Outpatient Setting
			▪ ED visits with hypoglycemia as first-listed diagnosis were identified using a validated algorithm. ▪ Estimates of population with diabetes from NHIS were used in the calculation of rates. ***CDC (National Health Interview Survey, NHIS)*** ▪ Estimates of civilian, non-institutionalized U.S. population with diabetes (denominator data that can be used for calculation of ADE rates)
National-, Regional-, Facility-level Spontaneous Reports	Voluntary reporting	***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
Regional-/ Facility-level ADE Incidence (+/- Rates)—Quality Improvement	Administrative claims and/or EHR data	***IHS (Resource and Patient Management System [RPMS-EHR])*** ▪ Adverse Reaction Tracking (ART) System entry related to a diabetes agent ▪ EHR entry in the Problem List of "hypoglycemia" ***VA (Integrated Databases):*** ▪ ADE identified by ICD-9-CM codes, primary hospitalizations, emergency department or clinic visits, and laboratory values (blood glucose, HbA1c). An algorithm has been developed and validated to identify hypoglycemia in VA patients.	***DOD (Pharmacovigilance Defense Application System):*** ▪ Outpatient clinic visits, ED visits, hospitalizations using relevant ICD-9-CM codes and/or CPT codes ***VA (Integrated Databases):*** ▪ ADE identified by ICD-9-CM codes, primary hospitalizations, emergency department or clinic visits, and laboratory values (blood glucose, HbA1c). An algorithm has been developed and validated to identify hypoglycemia in VA patients. ***IHS Resource and Patient Management System (RPMS-EHR)*** ▪ ART System entry related to a diabetes agent ▪ EHR entry in the Problem List or purpose of visit of "hypoglycemia"

*ICD-9-CM 962.3 refers to "Poisoning by insulins and antidiabetes agents," and E932.3 refers to "insulins and antidiabetic agents causing adverse effects in therapeutic use."
**Currently, FDA Sentinel initiative covers more than 125 million lives; however, these do not constitute a nationally representative sample.
***In 2015, MSPMS will be replaced by the Quality and Safety Review System (QSRS).
Abbreviations: ADE = adverse drug event; ART = adverse reaction tracking; CPT = Current Procedural Terminology; D50 = 50 percent dextrose; ED = emergency department; EHR = electronic health record; HbA1c = hemoglobin A1c; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; mg/dL = milligrams per deciliter; NHIS = National Health Interview Survey

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

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

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

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

Actions That Can Potentially Advance Surveillance Strategies for Diabetes Agent ADEs

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

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

Evidence-Based Prevention Tools

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

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

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

Resources for Safer Care—Health Care Provider Knowledge

- **AHRQ:**
  - **Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update**—Provides a systematic review of all oral diabetes medications, including evidence about the risk of hypoglycemia
- **BOP:**
  - **Management of Diabetes Clinical Practice Guidelines**—Provides recommendations for the medical management of Federal inmates with diabetes
- **DOD/VA:**
  - **Clinical Practice Guidelines for the Management of Diabetes**—Provides structured framework to help improve patient outcomes, along with evidence-based guidelines and identification of outcome measures
- **FDA:**
  - **Risk Evaluation and Mitigation Strategy**—Mandatory risk management plans that use risk minimization strategies beyond professional labeling to ensure that benefits of medications outweigh their risks
- **IHS:**
  - **Standards of Care and Clinical Practice Recommendations: Type 2 Diabetes**—Provides guidance to clinicians and educators with regularly updated recommendations, useful clinical tools and resources, patient education material and a bibliography
  - **Diabetes Treatment Algorithms**—Developed to provide clinicians with a quick reference based on national guidelines, these algorithms reflect a collaborative effort between Indian health system professionals. Cards can be accessed by mobile devices and/or printed for use in the clinical setting.
  - **Quick Guide Cards**—Summarize important elements of care, including the importance of individualized target setting for HgA1c
  - **Advancements in Diabetes Seminars**—Hour-long live virtual seminars that provide CME/CE credit and feature updates on appropriate treatment for patients with diabetes including practical tools
- **NIH:**
  - **National Diabetes Information Clearinghouse**—Information on diabetes blood tests

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

Resources for Patients and Family Engagement

- **ACL:**
  Community organizations offer various programs that have been or are currently supported in part by Federal funds, such as
  - **Stanford Diabetes Self-Management Program**—6-week program to help participants better manage their diabetes, including information about methods to deal with symptoms of hypoglycemia
  - **National Council on Aging Better Choices, Better Health-Diabetes**—6-week online workshop to learn self-management techniques, including curriculum on hypoglycemia
  - **HomeMeds℠ Medication Management System**—Multidisciplinary collaborative providing patient counseling, reassessment, and adjustment of medication regimens for older adults in various nonacute health care settings (e.g., home care)
- **AHRQ:**
  - **Medicines for Type 2 Diabetes: A Review of the Research for Adults**—Summary of research on benefits and possible side effects of diabetes agents to guide patients in discussions with their health care provider
  - **Premixed Insulin for Type 2 Diabetes: A Guide for Adults**—Guide compares benefits, side effects, and costs of a newer type of premixed insulin with other kinds of insulin and pills for diabetes
  - **Methods for Delivering Insulin and Monitoring Blood Sugar: A Review of the Research for Children, Teens, and Adults With Diabetes**—Discusses what research says about different ways to measure blood sugar and take insulin
- **FDA:**
  - **Medication Guides** (available for a variety of diabetes agents, including sulfonylurea-thiazolidinedione combination product)
- **NIH:**
  - **What I Need to Know About Diabetes Medicines**—Online resource which includes guidance on hypoglycemia
  - **Hypoglycemia**—Resource defining hypoglycemia, potential causes, treatment, and prevention (available in National Diabetes Information Clearinghouse)
  - **National Diabetes Information Clearinghouse**—Information on diabetes blood tests
- **NIH/CDC:**
  - **Know Your Blood Sugar Numbers**—Resource on how to test blood glucose level (produced by National Diabetes Education Program)

Resources for Communication and Coordination of Care

- **AHRQ:**
  - **Project RED**—Includes a number of medication-related strategies (e.g., active medication reconciliation, medication teaching for patients and caregivers, development of medication list for patients and their health care providers)
- **NIH/CDC:**
  - **Helping the Child with Diabetes Succeed: A Guide for School Personnel**—Resources for school personnel with guidance on preventing and treating hypoglycemia at school (produced by National Diabetes Education Program)

Inpatient settings

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

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

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

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

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

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

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

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

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

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

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

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

Patient and Family Engagement	▪ **Individualized target setting** – Acknowledgment of patient risk factors (e.g., BMI, cachexia, age, CHF, advanced malignancy, renal or liver disease) – Understand iatrogenic factors (e.g., nutritional intake, patient compliance, regimen change) ▪ **Educate patients on any self-management implications of changes to insulin regimen using teach back method** ▪ **Educate patients on use of products for treating low blood glucose, including over-the-counter products** [56] ▪ **Provide hypoglycemia diabetes patient education materials** ▪ **Understand patient adherence with medication and diet regimen and daily barriers that patients encounter** ▪ **Consider the use of a standardized process to assess individual patient need for devices for self-administration in the event of an urgent or emergent hypoglycemic event** [57]
Effective Communication and Coordination of Care	▪ **Multidisciplinary coordination and collaborative health care professional partnerships (including hospitalists, endocrinologists, nurses, pharmacists, and dietitians) throughout the medication process** [58, 59, 60, 61, 62] ▪ **Education of health care professionals on the importance of effective communication and coordination of care** ▪ **Engagement with pharmacists, nurses, dietitians, and other health care professionals at the time of discharge** ▪ **Minimize fragmentation of medical care** ▪ **Support development of tools that facilitate** – Improved prescribing of diabetes agents to minimize the potential for medication errors – Improved identification of root causes of hypoglycemic events – Improved patient compliance to/adherence with medication/diet and daily barriers that patients encounter

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

Science-Driven Prevention and Treatment	▪ **Consider individual patient characteristics in selecting diabetes agents and glycemic targets** ▪ **Use protocols to** – Assess risk during initial evaluation – Reassess risk periodically ▪ **Assess cause of prior events** ▪ **Support development of standardized tools for insulin administration (e.g., insulin infusion protocols)** ▪ **Ensure consistency in order sets** ▪ **Use standardized, evidence-based order sets (avoid free text)** ▪ **Conduct root cause analysis of hypoglycemic events when appropriate** ▪ **Capture critical information associated with hypoglycemic events at admission or discharge:** – Prior history of hypoglycemic episodes – Past diabetes medication management – Level of glycemic control – Assessment of patient's cognitive abilities, literacy level, visual acuity, dexterity, cultural context, and financial resources for acquiring outpatient diabetic medications and supplies
Promotion of Best Practices Within Communities	▪ **Encourage multidisciplinary care coordination** [31, 44] ▪ **Consider individual patient circumstances (e.g., cognition, life expectancy, sedation)** [31] ▪ **Ensure professional supervision during any medication changes**

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

Outpatient Settings

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

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

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

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

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

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

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

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

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

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

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

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

Safer Care	▪ Medication adjustments in response to changes in oral intake ▪ Coordination of meal time and blood glucose testing ▪ Care coordination across all health care professionals ▪ Medication reconciliation of diabetes medications ▪ Caution against use of sliding scale insulin in patients that may be at higher risk for hypoglycemia (e.g., older adults, those with dementia) ▪ Encourage a multidisciplinary care approach, including pharmacists, nurses, diabetes educators, dietitians ▪ Incorporate data from patient glucometers into the electronic health record to identify patients at risk
Patient and Family Engagement	▪ Tools to establish individual patient goals ▪ Shared decisionmaking, including patient preferences ▪ Teach-back method in which patient is asked to explain the clinician's instructions in his/her own words ▪ Train health care professionals on how to address cultural competency (literacy, language, cultural acceptability) ▪ Train health care professionals on how to address health literacy [58, 77, 78, 79, 80, 81, 82, 83] ▪ Awareness and education of patients/families on how to treat low blood glucose, including availability of products such as glucose tablets for home use [56] ▪ Understand patient compliance/adherence to medication and diet regimen and daily barriers patient encounters ▪ Explain risks of nocturnal hypoglycemia with patient and caregivers
Effective Communication and Coordination of Care	▪ Provider training on effective use of decision aids ▪ Education of health care professionals on the importance of effective communication and coordination of care ▪ Health care professionals should be encouraged to ask their patients if they experience any challenges with diet and encourage dietitians to be part of this process ▪ Enhanced medication reconciliation at the time of hospital discharge [84]

	▪ **Patient education** – Checking medication expiration date – Identification of home blood glucose goals – Detection and treatment of adverse events – Importance of consistent eating patterns – Guidance on sick day management – Information on accuracy of self-monitoring equipment

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

Science-Driven Prevention and Treatment	▪ **Development and enhancement of decision aids** [85] ▪ **Provider coordination of any changes in medication** ▪ **Addressing inaccuracy of self-monitoring of blood glucose with patients and caregivers** [86, 87, 88, 89]**
Promotion of Best Practices Within Communities	▪ **Multidisciplinary care coordination** [39, 40, 41, 51] ▪ **Consideration of individual patient circumstances (e.g., cognition, life expectancy, sedation)** [39, 40, 41, 51] ▪ **Professional supervision during any medication changes**

* Section 3506 of the Affordable Care Act encourages greater use of shared decisionmaking in health care and funds an autonomous program that would develop standards for and certify patient decision aids.
** The acceptable accuracy of these devices permitted by FDA is ±15 mg/dL of the results of the reference measurement at glucose concentrations <75 mg/dL or ± 20 percent at glucose concentrations >75 mg/dL [89]. International Standards Organization guideline permits ±15 mg/dL for values <75 mg/dl. Accuracy varies among meters [86, 87, 88], and additional error can be introduced by user parameters. These issues have recently been reviewed by the Food and Drug Administration [89].

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

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

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

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

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

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

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

Incentives and Oversight

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

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

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

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

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

Transitions of Care/Coordinated Care

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

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

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

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

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

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

Measure ID	Measure	Measure Description	Steward
NQF 0731	Comprehensive Diabetes Care**	This measure assesses the number of patients (18–75 years) who had each of the following: ▪ **Hemoglobin A1c (HbA1c) testing** ▪ HbA1c poor control (>9%) ▪ **HbA1c control (< 8%)** ▪ **HbA1c control (<7%) for subset of patients <65 years of age with exclusions for certain co-morbid conditions** ▪ Eye exam performed ▪ LDL-C screening ▪ LDL-C control (<100 mg/dL) ▪ Medical attention for nephropathy ▪ BP control (<140/90 mmHg) ▪ Smoking status & cessation advice	NCQA
NQF 0272	Diabetes Short-Term Complications Admission Rate	The number of discharges for diabetes short-term complications per 100,000 population over the past year	AHRQ***
NQF 0060	Hemoglobin A1c (HbA1c) testing for pediatrics	The percentage of pediatric patients with diabetes who received an HbA1c test	NCQA
NQF 1789	Hospital-Wide All-Cause Unplanned Readmission Measure	The measure estimates the hospital-level, risk-standardized rate of unplanned, all-cause readmission after admission for any eligible condition (including diabetes) within 30 days of hospital discharge	CMS

*Note: Measures summarized in this table are specific to diabetes medication management and diabetes-related hospital admissions or readmissions. Measures related to ensuring proper disease state management of diabetes that are not associated with risk of hypoglycemia are not shown here.
** NQF 0731 assesses comprehensive diabetes care that includes elements not specific to monitoring the risk of hypoglycemia.
*** Does not include admissions for hypoglycemia.
Abbreviations: HbA1c= hemoglobin A1c

Health Information Technology (Health IT)

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

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

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

Metric	Description and Justification
Clinical Quality Measure Concepts—Eligible Providers (Outpatient Settings)	
1. Percentage of patients on sulfonylurea/insulin therapy with out-of-range HbA1c	Assesses patients aged 65 and older with HbA1c <7% on sulfonylurea or insulin therapy with one of the following chronic co-morbidities: ▪ Cognitive impairment/dementia ▪ Advanced microvascular complications ▪ Limited life expectancy ▪ Current substance use
Rationale	Providers should be alerted when patients are at high risk for hypoglycemia.
Clinical Decision Support (CDS) Rule Concepts—Eligible Providers (Outpatient Settings)	
2. Alert to potential risk for hypoglycemic events	Clinical reminder to identify patients at high risk for hypoglycemic event
Rationale	Provider should be notified when a patient is high risk and either take action or comment on why no action was taken.
3. Shared decisionmaking on HbA1c glycemic goals	Clinical guidance that glycemic target should be discussed and set through dialogue between patient and provider and mutually agreed-on target range incorporated into medical record
Rationale	HbA1c glycemic goal should be entered in a field that can record use of shared decisionmaking to identify target.

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

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

Metric	Description and Justification
Clinical Quality Measure Concepts—Eligible Hospitals (Inpatient Settings)	
7. Hypoglycemic events, serious	Total number of hypoglycemic events, divided by the number of patients administered a diabetes agent
Rationale	Calculates percent of hypoglycemic events for all inpatients receiving diabetes agents.
8. Hyperglycemia	Total number of hyperglycemic hospital days (defined as elevated glucose level), divided by all individuals with a diagnosis of diabetes mellitus who were administered antidiabetic agents (except metformin)
Rationale	▪ Calculates percent of hyperglycemic events for all inpatients receiving diabetes agents. ▪ Serves as balancing measure to hypoglycemia measure.
9. Hypoglycemia, mild	Total number of days in which any hypoglycemic event (<70 mg/dL) reported, divided by total number of hospital days for patients receiving a diabetes agent
Rationale	Currently no system to effectively track and monitor episodes of hypoglycemia that do not result in need for third-party assistance.
10. Recurrent Hypoglycemia	Patients suffering at least one recurrent hypoglycemic event on a subsequent hospital day during the same hospital stay
Rationale	Patients suffering at least one recurrent hypoglycemic event on a subsequent hospital day during the same hospital stay.
EHR Functionality/Usability Recommendation—Eligible Hospitals (Inpatient Settings)	
11. Documentation of etiology of hypoglycemic event	Total number of hypoglycemic events, divided by all patients administered a diabetes agent

Rationale	Captures etiology and actions to take (checklist) to prevent future events
12. Alert to potential risk for hypoglycemic events	Clinical reminder and documentation of risk mitigation steps taken (checklist) when patient has experienced two or more blood glucose values of <70 mg/dL
Rationale	▪ When there is a patient with repeated blood glucose values of <70 mg/dL, provider should be alerted for potential risk. ▪ Provider should be provided list of options to prevent future episodes or document why no action taken.

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

Metric	Description and Justification
EHR Functionality/Usability Recommendation—Diabetes Agents Health Literacy/Numeracy (Inpatient & Outpatient Settings)	
13. Health literacy	Provision of patient education materials on diabetes medications that follow health literacy principles
Rationale	▪ Patients need educational materials that are easy to comprehend when prescribed a diabetes agent. ▪ Materials should follow health literacy principles. ▪ Materials should be available in patients' native language. ▪ Provider should ensure that the patient can understand and follow the materials.
14. Health numeracy	Test patient's ability to calculate numeric values to ensure proper HbA1c levels.
Rationale	▪ Critical to persons with diabetes self-management to avert potential harms ▪ Important when patient experiences changes in diet, exercise, or improper calculation of medication dose

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

Research (Unanswered Questions)

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

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

Actions That Can Potentially Advance Research Areas for Diabetes Agent Safety

Provider Education (***AHRQ, CDC, FDA, public–private partnerships)***

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

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

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

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

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

References

1. Centers for Disease Control and Prevention. National Diabetes Fact Sheet, 2011. Accessed April 7, 2014. Available from: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf
2. Adverse Drug Events: The magnitude of health risk is uncertain because of limited incidence data. GAO/HEHS-00-21. Available from: http://www.gao.gov/assets/230/228642.pdf. Accessed May 6, 2013.
3. Cox DJ, Gonder-Frederick L, Ritterband L, Clarke W, Kovatchev BP. Prediction of severe hypoglycemic events. *Diabetes Care* 2007; 30:1370–137.
4. Holstein A, Patzer OM, Machalke K, Holstein JD, Stumvoll M, Kovacs P. Substantial increase in incidence of severe hypoglycemic events between 1997-2000 and 2007-2010: a German longitudinal population-based study. *Diabetes Care*. 2012; 35(5):972-975.
5. Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ*. 2010; 340:b4909.
6. Warshaw G. Introduction: advances and challenges in care of older people with chronic illness. *Generation.* 2006; 30:5-10.
7. Punthakee Z, Miller ME, Launer LJ, Williamson JD, Lazar RM, Cukierman-Yaffee T, et al.; ACCORD Group of Investigators; ACCORD-MIND Investigators. Poor cognitive function and risk of severe hypoglycemic events in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. *Diabetes Care*. 2012; 35(4): 787-93.
8. Miller ME, Bonds DE, Gerstein HC, Seaquist ER, Bergenstal RM, Calles-Escandon J, et al.; ACCORD Investigators. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ*. 2010; 340: b5444.
9. De Galan BE, Zoungas S, Chalmers J, Anderson C, Dufouil C, Pillai A, et al.; ADVANCE Collaborative Group. Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. *Diabetologia*. 2009; 52(11): 2328-36.
10. Bonds DE, Miller ME, Dudl J, Feinglos M, Ismail-Beigi F, Malozowski S, et al. Severe hypoglycemic events symptoms, antecedent behaviors, immediate consequences and association with glycemia medication usage: Secondary analysis of the ACCORD clinical trial data. *BMC Endocr Disord*. 2012; 12: 5.
11. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009; 360(2):129-139.

12. Lipska KJ, Warton EM, Huang ES, Moffet HH, Inzucchi SE, Krumholz HM, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the Diabetes and Aging Study. *Diabetes Care.* 2013; 36(11):3535-42.

13. U.S. Department of Health and Human Services Office of Inspector General (OIG). Adverse events in hospitals: national incidence among Medicare beneficiaries. Washington, DC: 2010 November. Report No.OEI-06-09-00090.

14. Cook CB, Kongable GL, Potter DJ, Abad VJ, Leija DE, Anderson M. Inpatient glucose control: a glycemic survey of 126 U.S. hospitals. *J Hosp Med*. 2009;4(9):E7-E14.

15. Nirantharakumar K, Marshall T, Hodson J, Narendran P, Deeks J, Coleman JJ, et al. Hypoglycemia in non-diabetic in-patients: clinical or criminal?. PLoS ONE. 2012;7(7):e40384.

16. Wexler DJ, Meigs JB, Cagliero E, Nathan DM, Grant RW. Prevalence of hyper- and hypoglycemia among inpatients with diabetes: a national survey of 44 U.S. hospitals. *Diabetes Care*. 2007; 30(2):367-9.

17. Boord JB, Greevy RA, Braithwaite SS, Arnold PC, Selig PM, Brake H, et al. Evaluation of hospital glycemic control at US academic medical centers. *J Hosp Med*. 2009;4(1):35-44.

18. Matheny ME, Shubina M, Kimmel ZM, Pendergrass ML, Turchin A. Treatment intensification and blood glucose control among hospitalized diabetic patients. *J Gen Intern Med*. 2008;23(2):184-9.

19. Turchin A, Matheny ME, Shubina M, Scanlon JV, Greenwood B, Pendergrass ML. Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. *Diabetes Care*. 2009;32(7):1153-7.

20. Classen D, Jaser L, Budnitz D. Adverse drug events among hospitalized Medicare patients: epidemiology and national estimates from a new approach to surveillance. Joint Commission on Accreditation of Healthcare Organizations. 2010;36(1):12.

21. Institute for Safe Medication Practices. ISMP's list of high-alert medications. Available from: http://www.ismp.org/tools/highalertmedicationLists.asp. Accessed February 22, 2013.

22. Lewis AW, Bolton N, Mcnulty S. Reducing inappropriate abbreviations and insulin prescribing errors through education. *Diabet Med*. 2010;27(1):125-6.

23. Cousins D, Rosario C, Scarpello J. Insulin, hospitals and harm: a review of patient safety incidents reported to the National Patient Safety Agency. *Clin Med*. 2011;11(1):28-30.

24. Hellman R. A systems approach to reducing errors in insulin therapy in the inpatient setting. *Endocr Pract*. 2004;10 Suppl 2:100-8.

25. Deal EN, Liu A, Wise LL, Honick KA, Tobin GS. Inpatient insulin orders: are patients getting what is prescribed? *J Hosp Med*. 2011;6:526-9.

26. Cobaugh DJ, Maynard G, Cooper L, Kienle PC, Vigersky R, Childers D, et al. Enhancing Insulin-Use Safety in Hospitals: Practical Recommendations from an American Society of Healthsystems

Pharmacists (ASHP) Foundation Expert Consensus Panel. *Amer Society Health-Syst Pharm*. 2013;70:e18-27.

27. Budnitz D, Lovegrove M, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med. 2011*;365:2002-2012.

28. Lipska KJ, Ross JS, Wang Y, Inzucchi SE, Minges K, Karter AJ, et al. "National trends in hospital admissions for hyperglycemia and hypoglycemic events among medicare beneficiaries, 1999-2010." American Diabetes Association. 2013;Abstract 274-OR.

29. Sarkar U, Lopez A, Maseli J, Gonzales R. Adverse drug events in U.S. adult ambulatory medical care. *Health Services Research*, 2011;46(5):1517-1533.

30. Sarkar U, Karter A, Moffet H, Adler N, Schillinger D. Hypoglycemic events is more common among type 2 diabetes patients with limited health literacy: the Diabetes Study of Northern California (DISTANCE). *J Gen Intern Med*. 2010;25(9):962-968.

31. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384-95.

32. Cryer PE. Hypoglycemia in Diabetes: Pathophysiology, Prevalence and Prevention. Table 1.1, page 9. American Diabetes Association, Alexandria, Virginia, 2009.

33. Green AJ, Fox KM, Grandy S; SHIELD Study Group. Self-reported hypoglycemic events and impact on quality of life and depression among adults with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2012;96:313-318.

34. Centers for Medicare & Medicaid Services. CMS.gov research, statistics, data & systems. Available from: https://www.cms.gov/Research-Statistics-Data-and-Systems/Computer-Data-and-Systems/Minimum-Data-Set-3-0-Public-Reports/Minimum-Data-Set-3-0-Frequency-Report.html.

35. Chelliah A, Burge MR. Hypoglycaemia in elderly patients with diabetes mellitus: causes and strategies for prevention. *Drugs Aging*. 2004;21(8):511-30.

36. Abdelhafiz AH, Sinclair AJ. Hypoglycaemia in residential care homes. *Br J Gen Pract*. 2009;59(558):49-50.

37. Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. *Diabetes Care*. 2010;33(6):1389-94.

38. Ginde AA, Blanc PG, Lieberman RM, Camargo CA. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. *BMC Endocrinology Disorders*. 2008;8:4.

39. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35(6):1364-79.

40. American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control. *Endocr Pract*. 2009;15:1–17.

41. Lee SJ, Boscardin WJ, Stijacic cenzer I, Huang ES, Rice-trumble K, Eng C. The risks and benefits of implementing glycemic control guidelines in frail older adults with diabetes mellitus. *J Am Geriatr Soc*. 2011;59(4):666-72.

42. U.S. Department of Veterans Affairs, U.S. Department of Defense, 2010 Clinical Practice Guidelines: Management of Diabetes Mellitus in Primary Care. Available from: http://www.healthquality.va.gov/diabetes/.

43. The American Geriatrics Society. Choosing Wisely®: Five Things Physicians and Patients Should Question: An Initiative of the ABIM Foundation. Available from: http://www.americangeriatrics.org/health_care_professionals/clinical_practice/clinical_guidelines_recommendations/choosingwisely. Accessed on August 6, 2013.

44. American Diabetes Association. Standards of medical care in diabetes--2009. *Diabetes Care*. 2009;32 Suppl 1:S13-61.

45. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354(5):449-61.

46. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283-97.

47. American College of Physicians. American College of Physicians Issues Guideline for Use of Intensive Insulin Therapy for Management of Glycemic Control in Hospitalized Patients. Available from: http://www.acponline.org/pressroom/insulin.htm.

48. Michota F, Braithwaite SS. Avoiding complications in the hospitalized patient: the case for tight glycemic control. J Hosp Med. 2007;2 Suppl 1:1-4.

49. Braithwaite SS, Buie MM, Thompson CL, Baldwin DF, Oertel MD, Robertson BA, et al. Hospital hypoglycemia: not only treatment but also prevention. *Endocr Pract*. 2004;10 Suppl 2:89-99.

50. Maynard GA, Huynh MP, Renvall M. Iatrogenic inpatient hypoglycemia: risk factors, treatment, and prevention: analysis of current practice at an academic medical center with implications for improvement efforts. *Diabetes Spectrum*. 2008;21(4):241-247.

51. United States Department of Veterans Affairs. VA/DoD Clinical Practice Guidelines. Available from: http://www.healthquality.va.gov/.

52. Render ML, Freyberg RW, Hasselbeck R, Hofer TP, Sales AE, Deddens J, et al. Infrastructure for quality transformation: measurement and reporting in Veterans Administration intensive care units. *BMJ Qual Saf*. 2011;20(6):498-507.

53. Falciglia M, Freyberg RW, Almenoff PL, D'alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med*. 2009;37(12):3001-9.

54. Goldberg PA, Bozzo JE, Thomas PG, Mesmer MM, Sakharova OV, Radford MJ, et al. "Glucometrics"--assessing the quality of inpatient glucose management. *Diabetes Technol Ther*. 2006;8(5):560-9.

55. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA*. 2008;300:933-4.

56. Diabetes Forecast: The Healthy Living Magazine. Blood Glucose & Medications. Available from: http://www.diabetesforecast.org/landing-pages/lp-blood-glucose-and-medications.html

57. American Diabetes Association. Hypoglycemia (Low blood glucose). Available from: http://www.diabetes.org/living-with-diabetes/treatment-and-care/blood-glucose-control/hypoglycemia-low-blood.html.

58. Kripalani S, Roumie CL, Dalal AK, Cawthon C, Businger A, Eden SK, et al. Effect of a pharmacist intervention on clinically important medication errors after hospital discharge: a randomized trial. *Ann Intern Med*. 2012;157(1):1-10.

59. Kripalani S, Jackson AT, Schnipper JL, Coleman EA. Promoting effective transitions of care at hospital discharge: a review of key issues for hospitalists. *J Hosp Med.* 2007; 2:314–323.

60. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. *Ann Intern Med.* 2003;138:161–167.

61. Large BE. Providing timely discharge counseling. *Am J Health Syst Pharm*. 1999;56(11):1074,1076-7.

62. Lauster CD, Gibson JM, Dinella JV, Dinardo M, Korytkowski MT, Donihi AC. Implementation of standardized instructions for insulin at hospital discharge. *J Hosp Med*. 2009;4(8):E41-2.

63. Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A. Improving chronic illness care: translating evidence into action. Health Aff (Millwood). 2001;20(6):64-78.

64. Wagner EH. Chronic disease management: what will it take to improve care for chronic illness? Eff Clin Pract. 1998;1(1):2-4.

65. Piette JD. The impact of comorbid chronic conditions on diabetes care. *Diabetes Care*. 2006;29(3):725-731.

66. Lee EO, Emanuel EJ. Shared decision making to improve care and reduce costs. *N Engl J Med*. 2013;368(1):6-8.

67. Druss BG, Marcus SC, Olfson M, Tanielian T, Elinson L, Pincus HA. Comparing the national economic burden of five chronic conditions. *Health Aff. 2001*;*20*:*233*–241.

68. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med*. 2002;162(20):2269-76.

69. Maddigan SL, Feeny DH, Johnson JA. Health-related quality of life deficits associated with diabetes and comorbidities in a Canadian National Population Health Survey. *Qual Life Res. 2005;14*:*1311*–1320.

70. The Joint Commission. Look-alike/sound-alike drug list. Available from: http://www.jointcommission.org/LASA.

71. WHO Collaborating Centre for Patient Safety Solutions. Look-Alike, Sound-Alike Medication Names. *Patient Safety Solutions*. 2007;1(1). Available from: http://www.who.int/patientsafety/solutions/patientsafety/PS-Solution1.pdf.

72. Institute for Safe Medication Practices. ISMP's List of Confused Drug Names. Available from: http://www.ismp.org/Tools/confuseddrugnames.pdf.

73. Santiago JV. Nocturnal hypoglycemic events in children with diabetes: an important problem revisited. *J Pediatr.* 1997;131:2–4.

74. Standards for Outcomes Measurement of Diabetes Self-Management Education. *The Diabetes Educator*. 2003;29(5):804-816.

75. National Diabetes Education Program. Teens. Available from: http://ndep.nih.gov/teens/.

76. National Diabetes Education Program. Diabetes Resources for Schools and Youth. Available from: http://ndep.nih.gov/hcp-businesses-and-schools/Schools.aspx.

77. Agency for Healthcare Research and Quality. Topic: Health Literacy. Available from: http://www.ahrq.gov/health-care-information/topics/topic-health-literacy.html.

78. Morris NS, Maclean CD, Littenberg B. Literacy and health outcomes: a cross-sectional study in 1002 adults with diabetes. *BMC Fam Pract*. 2006;7:49.

79. Wolf MS, Williams MV, Parker RM, Parikh NS, Nowlan AW, Baker DW. Patients' shame and attitudes toward discussing the results of literacy screening. *J Health Commun*. 2007;12(8):721-32.

80. Cavanaugh K, Wallston KA, Gebretsadik T, Shintani A, Huizinga MM, Davis D et al. Addressing literacy and numeracy to improve diabetes care: two randomized controlled trials. *Diabetes Care*. 2009;32(12):2149-55.

81. Van Scoyoc EE, DeWalt DA. Interventions to improve diabetes outcomes for people with low literacy and numeracy: a systematic literature review. *Diabetes Spectrum*. 2010;23(4):228-237.

82. Schillinger D, Piette J, Grumbach K, Wang F, Wilson C, Daher C et al. Closing the loop: physician communication with diabetic patients who have low health literacy. *Arch Intern Med*. 2003;163(1):83-90.

83. Hawthorne K, Robles Y, Cannings-john R, Edwards AG. Culturally appropriate health education for Type 2 diabetes in ethnic minority groups: a systematic and narrative review of randomized controlled trials. *Diabet Med*. 2010;27(6):613-23.

84. Agency for Healthcare Research and Quality. Medications at Transitions and Clinical Handoffs (MATCH) Toolkit for Medication Reconciliation. Available from: http://www.ahrq.gov/professionals/quality-patient-safety/patient-safety-resources/resources/match/

85. United States Department of Veterans Affairs. Shared Decision Making with the Patient with Diabetes. Available from: http://www.healthquality.va.gov/diabetes/cpgSDMDMPOCKETFinalPRESS022513.pdf.

86. Ginsberg BH. Factors affecting blood glucose monitoring: sources of errors in measurement. *J Diabetes Sci Technol*. 2009;3(4):903-13.

87. Freckmann G, Schmid C, Baumstark A, Pleus S, Link M, Haug C. System accuracy evaluation of 43 blood glucose monitoring systems for self-monitoring of blood glucose according to DIN EN ISO 15197. *J Diabetes Sci Technol*. 2012; 6(5):1060-75.

88. Rebel A, Rice MA, Fahy BG. Accuracy of point-of-care glucose measurements. *J Diabetes Sci Technol*. 2012; 6(2):396-411.

89. Food and Drug Administration. FDA Evaluation of Point of care Blood glucose Meters. Available from: http://www.whitehatcom.com/POCWebMtgs/Slides/FDA_Evaluation_of_Blood_Glucose_Meters_D_Johnson_Lyles.pdf. Accessed August 7, 2013.

90. Pogach LM, Rajan M, Maney M, Tseng CL, Aron DC. Hidden Complexities in Assessment of Glycemic Outcomes Are quality rankings aligned with treatment?. *Diabetes Care.* 2010; 33(10): 2133-2139.

91. HealthIT.gov. Policy: Quality Measures Workgroup. Available from: http://www.healthit.gov/facas/calendar/2013/06/03/policy-quality-measures-workgroups.