A Systematic Review of Insulin Adherence Measures in Patients with Diabetes

Samuel Stolpe, PharmD; Michel A. Kroes, MSc; Neil Webb, BSc Hons; and Tami Wisniewski, MPH

ABSTRACT

BACKGROUND: Diabetes care is associated with a considerable burden to the health care system in the United States, and measuring the quality of health care is an important development goal of the Department of Health and Human Services and the Centers for Medicare & Medicaid Services. Diabetes is a priority disease within the National Quality Strategy and should therefore remain a focus in the measurement of health care quality. Despite the importance of measuring quality in diabetes care management, no quality measure is currently associated with adherence to insulin treatment, and measuring adherence to insulin is known to be complicated.

OBJECTIVES: To (a) identify methods to measure insulin adherence in patients with diabetes and (b) evaluate whether identified methods could be considered for testing as a quality measure.

METHODS: Systematic searches were conducted in the online electronic databases Embase, MEDLINE, and the Cochrane Library, supplemented with additional manual searches to identify publications on insulin adherence from the year 2000 onward. Identified citations were screened for relevance against predefined eligibility criteria, and methods to measure adherence to insulin were extracted from relevant studies into data extraction tables. Methods were critiqued on the feasibility for consideration as a quality measure.

RESULTS: Seventy-eight publications met the inclusion criteria and were reviewed. Included studies reported various indirect methods to measure adherence to insulin, using prescription claims or self-report questionnaires. Commonly reported methods included the (adjusted) medication possession ratio, proportion of days covered, persistence, daily average consumption, and the Morisky Medication Adherence Scale. All types of identified methods were associated with measuring challenges varying from accuracy of estimated adherence, complexity of data collection, absence of validated threshold for good adherence, and reliability of adherence outcomes.

CONCLUSIONS: Without additional research, none of the identified methods are appropriate for use as a quality measure for insulin adherence. We suggest patient involvement in future research and additional quality measure development.

J Manag Care Spec Pharm. 2016;22(11):1224-46

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- Quality of care delivered is a key aspect of current U.S. health care reform plans and diabetes is considered a priority disease, with metrics being developed to measure the quality of health care delivered.

What this study adds

- This article provides an overview and critique of methods used to measure adherence to insulin in the context of development of quality measures in the United States.
- While there is some potential based on previously developed methods to measure insulin adherence, without additional research, none of the identified methods are currently appropriate for use as a quality measure for insulin adherence.

Diabetes is a chronic metabolic disorder characterized by elevated blood glucose levels (hyperglycemia) and is associated with considerable morbidity and mortality. Type 1 diabetes mellitus (T1DM) is an autoimmune disease in which there is failure by pancreatic islet β -cells to produce insulin. The American Diabetes Association recommends that T1DM be treated with multiple-dose insulin injections (3 to 4 injections per day of basal and bolus insulin), or continuous subcutaneous insulin infusion.¹ Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance with progressive loss of β -cell function and subsequent insulin deficiency. Risk factors for T2DM include obesity, diet, sedentary living, family history of diabetes, and race/ethnicity, to name a few. T2DM is a progressive disease and treatment is intensified with disease progression. Many patients with T2DM will eventually require insulin to control their blood glucose levels, and many patients will need to intensify their treatment regimens over time.²

Treatment adherence is critical to effective management of T1DM and T2DM. Adherence to insulin treatment has been associated with improved levels of glycemic control,³ which reduces the risk of developing micro- and macro-vascular complications⁴ and all-cause mortality.⁵ However, poor adherence to insulin regimens is common in people with diabetes.⁶ The 2 most commonly reported difficulties with insulin treatment, as reported by both patients and physicians, are the requirements for multiple injections and adherence to prescribed dosing times.⁷ Fear of hypoglycemia,^{8,9} weight gain,^{9,10} and treatment complexity⁶⁻⁹ are additional barriers to good adherence to

What is already known about this subject

- A considerable proportion of patients with diabetes use insulin, particularly those with advanced disease.
- Good adherence to insulin treatment as prescribed is important in managing diabetes; however, it is difficult to measure adherence levels to injectable medication.

insulin treatment. In 2010, Cooke et al. reported that persistence with injectable insulin 12 months after initiation was as low as 28.7% in a U.S. population of patients with T2DM.¹¹

With an estimated prevalence of 14.3% in 2011-2012, diabetes costs the United States approximately \$245 billion annually.¹² The combination of high prevalence and cost of diabetes has resulted in increased attention to appropriate care and control of patients with diabetes among both public and private payers. This increased attention has manifested in the development and implementation of several quality measures intended to ensure adequate disease control at the population level. Table 1 describes current diabetes quality control measures endorsed by the National Quality Forum (NQF). A Pharmacy Quality Alliance (PQA) measure that addresses adherence to diabetes medications is currently being used within the Centers for Medicare & Medicaid Services (CMS) Star Ratings for Medicare Parts C and D and in the Health Insurance Exchanges Quality Rating System. Through a consensus-based process, PQA endorsed the proportion of days covered (PDC) method, which is currently considered the measurement standard for adherence to oral medications.¹³

The PQA diabetes medication adherence measure does not include insulin due to feasibility challenges associated with prescription claims data and injectable medication days supply. This is an important challenge to address because approximately 30% of patients with diabetes, and those with the most advanced disease, are treated with insulin.¹⁴ Following the passage of the Patient Protection and Affordable Care Act in 2010, which aimed to reduce health care costs while preserving or enhancing the quality of health care delivered, it has become increasingly apparent that there is a need for a standardized approach to measure insulin adherence.

Given the known complexity of measuring adherence to injectable treatments and the lack of a quality measure that assesses adherence to insulin in federal quality measurement programs, we conducted a systematic review (SR) to understand the evidence base associated with methods to measure adherence to insulin in patients with diabetes. Our purpose was to identify potential methods that could be considered for further investigation as a quality measure suitable for public-facing performance programs and value-based payment structures.

Methods

An SR was conducted to identify studies reporting methods to measure adherence to self-injectable treatments in patients with diabetes, rheumatoid arthritis, multiple sclerosis, or human immunodeficiency virus, or in those requiring human growth hormone. Here we present the subset of findings relating to methods of measuring adherence to insulin in patients with diabetes.

Search Methods for Identification of Studies

The following electronic databases were searched using Ovid: Embase, MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, and the Cochrane Library. Only English language publications published from the year 2000 onward were searched.

Search strings are provided in the Appendix (available in online article). The search was run on November 24, 2014, and updated on June 29, 2015. In addition, conference proceedings of interest were searched between 2012 and 2015. Additional supplementary searches included the websites of the NQF database, the Health and Human Services (HHS) Measures Inventory, the Agency for Healthcare Research and Quality National Quality Measures Clearinghouse, and the Health Indicators Warehouse.

Eligibility Criteria

Key eligibility criteria were recorded a priori in a review protocol (not registered) and are presented in Table 2. Studies were included if participants were adults (aged ≥ 18 years) with diabetes (type 1 or type 2, as defined by study, typically by *International Classification of Diseases, Ninth Revision, Clinical Modification* codes), and measurement of insulin adherence was clearly described. Randomized controlled trials (RCTs) were excluded, as they are protocol driven and may not provide generalizable accurate methods for measuring insulin adherence in the real world for quality reporting purposes.

Data Collection and Analysis

Citations identified through the searches were assessed by a reviewer (author Webb) based on title and abstract using the predefined eligibility criteria. Full publications of potentially relevant citations were obtained and examined by 2 reviewers (Webb and author Kroes). Disputes were resolved via discussion with third parties (authors Wisniewski and Stolpe). Relevant data from eligible publications were extracted into a data extraction table by a reviewer (Webb) and verified by a second reviewer (Kroes).

Included studies were evaluated for risk of bias using the Newcastle-Ottawa scale (NOS)¹⁵: a “star system” to assess the quality of nonrandomized studies on 3 perspectives: selection of study groups; comparability of groups; and ascertainment of exposure or outcome of interest for case-control or cohort studies, respectively.

Results

Study Selection

A diagram illustrating the flow of citations through the SR process is provided in Figure 1. A total of 4,845 citations were identified in the full search. Seventy-eight publications reporting insulin adherence measures in adults (aged ≥ 18 years) with T1DM or T2DM were included in the final dataset.

TABLE 1 Summary of Implemented NQF-Endorsed Diabetes Quality Measures in the United States

Quality Measure Outcome of Interest	Measure Description	Quality Programs Using the Measure
A1c	Percentage of children aged 5 to 17 years with diabetes (types 1 and 2) who had an A1c test during measurement year	• Meaningful Use
	Percentage of members aged 18 to 75 years with diabetes (types 1 and 2) who had A1c control (<8.0%)	• HEDIS
	Percentage of patients aged 18 to 75 years with diabetes (types 1 and 2) who received an A1c test during the measurement year	• Medicaid Adult Core Set
	Percentage of patients aged 18 to 75 years with diabetes who had A1c >9.0% during the measurement year	• MA Star Rating • HEDIS • Meaningful Use • MSSP • PQRS
Blood pressure	Percentage of members aged 18 to 75 years with diabetes (types 1 and 2) whose most recent blood pressure reading is <140/90 mm Hg during the measurement year	• MA Star Rating • HEDIS
	Percentage of patients who were dispensed medication for diabetes and hypertension who are receiving an ACE inhibitor or ARB or DRI renin-angiotensin antagonist	• MA Star Rating
LDL	Percentage of members aged 18 to 75 years with diabetes (types 1 and 2) who received an LDL cholesterol test during the measurement year	• Medicaid Adult Core Set • MA Star Rating
	Percentage of patients aged 18 to 75 years with diabetes whose LDL cholesterol was adequately controlled (<100 mg/dL) during the measurement period	• MA Star Rating • HEDIS • Meaningful Use • PQRS
Foot exam	Percentage of patients aged 18 to 75 years with diabetes who had a foot exam during the measurement period	• HEDIS • Meaningful Use • MSSP • PQRS
Eye exam	Percentage of patients aged 18 to 75 years with diabetes who had a retinal or dilated eye exam by an eye care professional during the measurement period or a negative retinal exam (no evidence of retinopathy) in the 12 months prior to the measurement period	• MA Star Rating • HEDIS • Meaningful Use • PQRS
Coronary artery disease	Percentage of patients aged ≥18 years with a diagnosis of coronary artery disease seen within a 12-month period who also have diabetes or a current or prior LVEF <40% who were prescribed ACE inhibitor or ARB therapy	• MSSP • PQRS
Foot and ankle care	Percentage of patients with diabetes aged ≥18 years with a diagnosis of diabetes mellitus who had a neurological examination of their lower extremities during 1 or more office visits within 12 months	• PQRS
	Percentage of patients aged ≥18 years with a diagnosis of diabetes mellitus who were evaluated for proper footwear and sizing during 1 or more office visits within 12 months	• PQRS
Short-term complications admission rate	Admissions for a principal diagnosis of diabetes with short-term complications (ketoacidosis, hyperosmolarity, or coma) per 100,000 population aged ≥18 years. Excludes obstetric admissions and transfers from other institutions	• Medicaid Adult Core Set
Diabetic retinopathy	Percentage of patients aged ≥18 years with a diagnosis of diabetic retinopathy who had a dilated macular or fundus exam performed with documented communication to the physician who manages the ongoing care of the patient with diabetes mellitus regarding the findings of the macular or fundus exam at least once within 12 months	• Meaningful Use • PQRS
	Percentage of patients aged ≥18 years with a diagnosis of diabetic retinopathy who had a dilated macular or fundus exam performed that included documentation of the level of severity of retinopathy and the presence or absence of macular edema during 1 or more office visits within 12 months	• Meaningful Use • PQRS
Nephropathy	Percentage of patients aged 18 to 75 years with diabetes who had a nephropathy screening test or evidence of nephropathy during the measurement period	• MA Star Rating • HEDIS • Meaningful Use • PQRS
Optimal diabetes care	Percentage of adult diabetes patients who have optimally managed modifiable risk factors (A1c, blood pressure, statin use, tobacco nonuse and daily aspirin or antiplatelet use for patients with diagnosis of ischemic vascular disease) with the intent of preventing or reducing future complications associated with poorly managed diabetes. Patients aged 18-75 years with a diagnosis of diabetes who meet all the numerator targets of this composite measure: A1c <8.0, LDL <100, blood pressure <140/90, tobacco nonuser and for patients with diagnosis of ischemic vascular disease daily aspirin use unless contraindicated	• PQRS
Taking diabetes medication as directed	Percentage of patients ≥18 years who met the PDC threshold of 80% during the measurement year. A performance rate is calculated separately for the following medication categories: RAS antagonists, diabetes medications, statins.	• MA Star Rating

A1c = hemoglobin A1c; ACE = angiotensin-converting enzyme (inhibitor); ARB = angiotensin receptor blocker; DRI = direct renin inhibitor; HEDIS = Healthcare Effectiveness Data and Information Set; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MA = Medicare Advantage; MSSP = Medicare Shared Savings Program; NQF = National Quality Forum; PDC = proportion of days covered; PQRS = Physician Quality Reporting System; RAS = renin-angiotensin system.

TABLE 2 Eligibility Criteria for the Systematic Review

Criteria	Include	Exclude
Population	Adults (aged ≥18 years) with type 1 or type 2 diabetes as defined in study	<ul style="list-style-type: none"> • Pediatric populations • Studies reporting only results for mixed populations (i.e., part of the population not meeting the inclusion criteria)
Intervention & comparators	<ul style="list-style-type: none"> • Insulin 	<ul style="list-style-type: none"> • Studies reporting on adherence measures of mixed treatments
Outcomes	<ul style="list-style-type: none"> • Methods to measure adherence to insulin 	<ul style="list-style-type: none"> • Studies reporting only adherence outcomes/rates without reporting methods of how these were measured
Study design	<ul style="list-style-type: none"> • Observational studies • Database claims analyses • Modeling studies 	<ul style="list-style-type: none"> • Randomized controlled trials • Reviews • Letters, editorials, news • Case studies on a single case

Most studies used retrospective claims cohorts, were conducted in the United States (61 studies), and were industry sponsored. The majority (58 studies) included patients with T2DM, 2 included T1DM patients, 10 included both, and the remaining did not report diabetes type. The mean population age ranged between 37.4 and 74.6 years. Most studies investigated any insulin treatment, with insulin type not specified, and the time period of most analyses was 1 year. The overall quality of the cohort studies was generally high, with many achieving 7 stars when using the NOS.

Adherence Measures Commonly Reported

Table 3 lists the adherence measures most commonly reported, their definitions, and areas of divergence between studies. The main areas of divergence were the denominator used when calculating the medication possession ratio (MPR), the definition of the refill gap while measuring persistence, and the additional assumptions used when calculating the PDC (e.g., imputation of missing days supply). Although not generally considered a direct measure of adherence, daily average consumption (DACon) was reported in 12 studies alongside the methods described above, and usually only for those patients established as adherent. All identified methods to measure adherence were indirect, with no studies identified that measured adherence directly through observation of medication taking, return of device used to inject the medication, or biological fluid samples.

Medication Possession Ratio. Twenty-two studies measured adherence using MPR.¹⁶⁻³⁷ The numerator used to calculate MPR was consistent in 21 studies,^{16-19,21-37} whereas the denominator varied. Denominators included number of days between first fill and last fill in 2 studies^{17,32}; between first and last fill plus the days supply of the last fill in 3 studies^{19,27,29}; from first fill date to either the end of the last day of supplied medication during the study period or the end of the study period (whichever came first) in 1 study³³; and the analysis period in 15 of the studies.^{16,18,21-26,28,30,31,34-37} Table 3 shows a summary of the denominators used. In 1 study, the method used to calculate the MPR was not reported.²⁰

Adjusted Medication Possession Ratio. An adjusted MPR was used in 11 studies to account for potential difference in pack sizes across pens and vials.^{30,31,35-43} Adjusted MPRs were calculated by analyzing the distribution of data by product and method of administration. The observed MPR was multiplied by the ratio of either the mean (N = 10 studies) or median (N = 1 study) time between claims divided by the mean or median pharmacy reported days supply. Five of the studies reported adherence rates using both the traditional and adjusted MPR method.^{35-38,42} Comparison of both methods showed that the adherence increased when measured using the adjusted MPR.^{35-38,42} In Grabner et al. (2013), adherence was similar between pen and vial cohorts when measured using the traditional MPR method; however, when measured according to adjusted MPR, adherence was statistically significantly different between groups ($P < 0.001$).⁴²

Proportion of Days Covered. Ten studies measured adherence using the PDC.⁴⁴⁻⁵³ PDC was measured using the traditional method in 8 studies,^{44,46-49,51-53} and in 1 study PDC methodology was not reported.⁵⁰ In Donnelly et al. (2007), the authors used a method resembling PDC, although it was not specifically termed PDC.⁴⁵

Assumptions were reported in several PDC studies. Consistent with the PDC approach, which prohibits the possibility of having a PDC > 1, 4 studies reported appending days of overlap to the previous prescription's end, where overlaps existed.^{49,51,53,54} In Lee et al. (2011), data on the days supply were missing and therefore, the average days supply was imputed.⁴⁹ In Gibson et al. (2010), if a patient switched medication within a therapeutic class, it was assumed the remainder of the previous prescription was discarded and coverage commenced with the supply of the new medication. It was also assumed that days in hospital were considered adherent days. To account for the potential that the days supply of insulin might not indicate the full extent of coverage, a multiplier to reflect the average time between insulin prescriptions was applied.⁴⁸ In both Eby et al. (2013) and Eby et al. (2014), 2 variations from the traditional PDC method were applied. The first calculated PDC based on the proportion of days when

FIGURE 1 Flow Diagram of Included Studies

SR=systematic review.

a minimum of each patient's index daily dose was available (PDCindex).^{46,47} The second analysis, which aimed to describe the level of adherence to high-dose regimens, calculated PDC based on the proportion of days for which >200 units/day of insulin were available (PDC200) in Eby et al. (2013)⁴⁶ and the proportion of days for which ≥150 units/day of insulin were available (PDC150) in Eby et al. (2014).⁴⁷

Persistence. A total of 23 studies (24 publications) reported on methods to measure persistence with treatment.^{11,17,24,30,31,35-37,39-43,54-64} Fifteen studies (65%) used the same method to measure treatment persistence^{30,31,35-37,39,41-43,56,58-61,64}; the percentage of patients who did not discontinue their treatment, with medication considered discontinued if the

prescription was not filled within an expected time of medication coverage. Whereas there was a consistent definition to the expected time of medication coverage (a percentile of the time, stratified by the metric quantity supplied, between the first and second fills among patients with at least 1 refill), the percentile of time varied across studies. Eleven studies used the 90th percentile of time (sensitivity analysis: 75th and 95th percentile of time).^{30,31,35-37,39,42,43,60,61,64} Three studies used the 75th percentile of time (sensitivity analyses: 50th and 90th percentile of time),^{56,58,59} and 1 study used the 75th percentile of time (sensitivity analysis: 90th and 95th percentile of time).⁴¹ When measuring the percentage of patients discontinuing treatment, the number of persistent days (number of days between the index date and the discontinuation/switch date) was also calculated.

TABLE 3 Most Commonly Reported Adherence Measures

Adherence Measures	Calculation Method	Number of References Using This Measure	Areas of Divergence	Adherence Measure Advantages and Disadvantages
Medication possession ratio	Using prescription data from pharmacy claims $\text{MPR} = \frac{\text{Total days supply of all prescriptions in defined period}}{\text{Number of days in the defined period}}$ Value between 0 and 1, 1 being 100% adherent Patients are usually considered adherent at an $\text{MPR} \geq 0.8$ (80%). ¹⁸	n = 22 ¹⁶⁻³⁷	Denominator as number of days from first fill until last fill or 1 year or otherwise modified (e.g., excluding days hospitalized or overlap in fills)	Advantages: <ul style="list-style-type: none"> • Uses pharmacy claims data • Relatively easy to calculate Disadvantages: <ul style="list-style-type: none"> • Presence of pharmacy claim does not indicate medication taken • Can overestimate adherence if patients refill prescriptions early • Pharmacy claims data affected by wastage and stockpiling • Relies on days supply in calculation
Adjusted medication possession ratio method	Using prescription data from pharmacy claims $\text{Adjusted MPR} = \text{MPR} \times \frac{\text{Average days between prescription refills}}{\text{Average days supply}}$ Used to account for the differences in pack sizes between insulin devices	n = 11 ^{30,31,35-43}	Correct the issue that almost all prescriptions are dispensed with a 30-day supply period even though patients may have more insulin than ordered due to variations in their daily dosing (dependent on body weight and glycemic control). ³⁵	Advantages: <ul style="list-style-type: none"> • Uses pharmacy claims data • Ability to adjust for differences in insulin pack sizes and correct for prescriptions dispensed with 30-day supply period Disadvantages: <ul style="list-style-type: none"> • Pharmacy claims data affected by wastage and stockpiling • Adjustment factor not standardized • Relies on days supply in calculation
Proportion of days covered	Using prescription data from pharmacy claims $\text{PDC} = \frac{\text{Days supplied between first and last prescription}}{\text{Days between first fill and end of the measurement period}}$ Patients are usually defined as adherent if they have a $\text{PDC} \geq 80\%$. ⁶⁵ Endorsed by the PQA as the preferred method for measuring medication adherence ⁴⁴	n = 10 ⁴⁴⁻⁵³	Can adjust for overlapping prescriptions, different types of medication and adjust for proportion of days spent in hospital. When calculating the PDC for a single drug, it can be considered the same as the MPR measure that is calculated using the full analysis period as the denominator, if the MPR is capped at 1. ⁴⁹	Advantages: <ul style="list-style-type: none"> • Uses pharmacy claims data • Method endorsed by the PQA as preferred method for measuring adherence • Accounts for overlap in days supply • More accurate when calculating adherence to medication regimens Disadvantages: <ul style="list-style-type: none"> • Does not account for differences in insulin pack size • Pharmacy claims data affected by wastage and stockpiling • Relies on days supply in calculation
Persistence	Using prescription data from pharmacy claims: Patient remaining on the study drug for the entire follow-up period without discontinuation or switching after initiation of the index drug	n = 24 ^{11,17,24,30,31,35-37,39-43,54-64}	Time between refills (gaps) and proportion of patients not refilling in time	Advantages: <ul style="list-style-type: none"> • Uses pharmacy claims data • Assesses treatment discontinuation Disadvantages: <ul style="list-style-type: none"> • Pharmacy claims data affected by wastage and stockpiling • Measure indicates patient is persistent but does not measure compliance with physician's recommendations • A predefined treatment gap is not suitable for measuring persistence with injectables due to variable-dose titration schedules
Daily average consumption	Using prescription data from pharmacy claims $\text{DACON} = \frac{\text{Total number of units dispensed}}{\text{Number of days between index date and date of last fill}}$ where Total units dispensed = total milliliters dispensed for all prescriptions in follow-up period $\times 100$ No benchmark exists for DACON representing good adherence.	n = 12 ^{30,31,36-39,41-43,56,60,64}	Can adjust for units dispensed and can account for type of insulin administered when interpreting results	Advantages: <ul style="list-style-type: none"> • Uses pharmacy claims data • Accounts for differences in insulin pack size • Easily calculated • Avoids use of days supply Disadvantages: <ul style="list-style-type: none"> • No validated threshold for good adherence • Pharmacy claims data affected by wastage and stockpiling • Inter- and intrapersonal variability could confound results in large datasets

TABLE 3 Most Commonly Reported Adherence Measures (continued)

Adherence Measures	Calculation Method	Number of References Using This Measure	Areas of Divergence	Adherence Measure Advantages and Disadvantages
Morisky Medication Adherence Scale	Patient self-report measures with 4 or 8 items that can be scored as either yes (0) or no (1) MMAS-4 scores: 0=high adherence; 1-2=medium adherence; 3-4=low adherence MMAS-8 scores: 0=high adherence; 1-2=medium adherence; 3-8=low adherence ⁶⁶	MMAS-4 n = 6 ⁶⁷⁻⁷² and MMAS-8 n = 3 ⁷³⁻⁷⁵	Not applicable	Advantages: <ul style="list-style-type: none"> Can be used to gather information on reasons for nonadherence Self-reported surveys often increase compliance, as the individuals know they are being observed Disadvantages: <ul style="list-style-type: none"> Self-reported measure where patients may be dishonest Complexity and cost of data collection when implementing as a quality measure

DACON=daily average consumption; MMAS=Morisky Medication Adherence Scale; MPR=medication possession ratio; PDC=proportion of days covered; PQA=Pharmacy Quality Alliance.

In Buysman et al. (2011), a similar method of using the expected time of medication coverage was used to measure persistence. However, in this study, an adjustment factor was used when measuring persistence to account for variations in insulin pack size and dosing schedules.⁴⁰ An adjustment factor was calculated as the ratio of the 80th percentile of time between insulin claims divided by the 80th percentile of the pharmacy-reported days supply. The adjustment factor was then multiplied by the actual days supply reported on the pharmacy claim to calculate an adjusted days supply, and patients with a gap of 1 or more days in insulin therapy based on the adjusted days supply were defined as discontinuing therapy.⁴⁰

In the remaining 7 studies, patients were considered non-persistent with therapy if the time without treatment was of a predefined length.^{11,17,24,44,55,57,62} In Rashid et al. (2012), this measure was defined as the time to all-cause discontinuation, and a predefined gap of 90 days without any drug supply available was considered discontinuation.⁶² The following gaps were used in other included studies: 60 and 90 days,²⁴ 60 days,⁴⁴ and 30 days.^{17,55} In Bonafede et al. (2011), persistence was calculated using 2 measures: if there was a 90-day gap in prescription fills, or if a specific number of refills did not occur within a prespecified time period.⁵⁷

Daily Average Consumption. A total of 12 studies measured DACON.^{30,31,36-39,41-43,56,60,64} All 12 studies used the traditional DACON method, with no studies applying additional assumptions. An expected level/benchmark of DACON or a threshold at which patients would be considered adherent was not reported. No studies reported a comparison of DACON among the adherent compared with the nonadherent.

Morisky Medication Adherence Scale. The Morisky Medication Adherence Scale (MMAS)-4 questionnaire was used to assess adherence in 6 of the included studies.⁶⁷⁻⁷² The

MMAS-8 questionnaire was used to assess adherence in 3 of the included studies.⁷³⁻⁷⁵

Other Adherence Measures

In 20 studies, methods other than those described in Table 3 were used to measure adherence (data not shown).^{7,76-94}

Discussion

This SR was designed to identify studies reporting methods to measure adherence to insulin treatment in patients with diabetes. Previous SRs have studied adherence to diabetes medication, but to our knowledge this is the first to focus specifically on methods to measure adherence to insulin in adults with diabetes for the purpose of consideration for a quality performance measure. Cramer et al. (2004) conducted an SR to determine the extent to which patients omit doses of medications prescribed for diabetes.⁹⁵ However, as commented by Wens et al. (2004), an important database, Embase, was not searched in that SR, and therefore important studies may have been omitted.⁹⁶ Other previous SRs focused on adherence rates,⁹⁷ factors affecting adherence,^{98,99} improving adherence,¹⁰⁰⁻¹⁰³ or assessed adherence with oral medications only.^{104,105} One SR published in 2014 reviewed methods to measure medication adherence in patients with diabetes on oral hypoglycemic agents and/or insulin in original research published between 2007 and 2013.¹⁰⁶ The scope of our SR differed by excluding pediatric populations, oral medication, or RCTs as study design and includes publications since the year 2000. To our knowledge, none of the SRs aforementioned had the same objective.

Limitations

The SR was conducted using predefined eligibility criteria and conformed to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,¹⁰⁷ which contributes

to the robustness of the conclusions. There were some limitations in the SR methodology. The searches were restricted to identify only those studies published after the year 2000. Searches were limited to 2000 onward, as outcomes research and quality measures for adherence would not have been studied in great depth or available to patients before this date.¹⁰⁸

A factor influencing the generalizability of the data is the inclusion of studies that used databases, such as the PharMetrics database, the Thomson Reuters MarketScan database, and the Innovus IMPACT national managed care database. These studies used specific patient populations, and the data from these studies may not be generalizable to other populations.

Challenges with Measuring Insulin Adherence

There are advantages and disadvantages associated with the different methods to measure insulin adherence, which should be considered when assessing their applicability as a quality measure.

The MPR and PDC methods allow different ways to calculate the supply and possession of medication based on pharmacy claims data. The key strength of the adjusted MPR and adjusted PDC over the traditional MPR and PDC is the ability to adjust for differences in insulin pack sizes, and to correct for the fact that almost all insulin prescriptions are dispensed with a 30-day supply period even though patients may have more insulin than ordered due to variations in their daily dosing. This adjustment allows for a more accurate representation of how a patient adhered to the prescription as written by the prescriber. However, insulin adherence calculations from prescription claims data are particularly challenging, as such calculations are performed based on the days supply entered by the pharmacist during claim submission and adjudication. The days supply used for billing often does not match the clinically appropriate days supply because of issues such as irregular insulin dosing, sliding scale usage, and unit-based dispensing. While the reliability of the days supply primarily persists with pens, assuming a 28-day supply for vials because they should not be used beyond that due to shelf life limitations, is equally problematic from a quality measure perspective, as it is an additional assumption that would need to be made in any analysis.

Persistence can also be measured with pharmacy claims data. As described in the results, similar adjustment factors have been applied to persistence and adherence. The challenge with the use of any adjustment factor, whether associated with MPR, PDC, or persistence, is that the method is not entirely standardized because the adjustment factor is contingent on the distribution of each product and formulation within the population of interest. While this is feasible from the research perspective, it may be problematic when financial incentives or penalties are applied if a given insurance plan does or does not meet the metric.

We suggest that an adjusted MPR, PDC, or persistence analysis would need to be validated before considering use as a performance measure. Additionally, a cross-validation technique would need to be developed that could be applied randomly when used as part of performance measurement to minimize potential for human error due to the nonstandardized approach. In the interim, researchers should perform and report sensitivity analyses based on the distribution of data that informs any adjustments. In the case of PDC or MPR, analyses that adjust for both mean and median days supply and/or analyses that consider the lower and upper bounds of the 95% confidence interval when the mean is applied may be appropriate. For persistence, sensitivity analyses that consider a minimum 10% variation in the percentile of time period analyzed may be appropriate.

The insulin consumption as measured with DACON accounts for dose consumed; however, a limitation specifically with DACON is the lack of a validated threshold for good adherence. A large population with inter- and intrapersonal variability in insulin types and dose requirements complicates generalization of consumption requirements. Whereas DACON is traditionally measured over a persistent time period, it may be worth investigating whether a redefinition of the time period of interest is warranted in this context. For example, if DACON were calculated over a calendar year of interest rather than a persistent period of interest, it may be possible to identify a minimum threshold that correlates with both persistency and diabetes control (measured by hemoglobin A1c). While this hypothesis would need to be tested before further consideration of a revised DACON as a means to approximate adherence for performance measurement purposes, the objectivity of the DACON value is reassuring.

The measures using pharmacy claims data may be more reliable than those recorded from self-report questionnaires (such as MMAS), as the latter may be subject to reporting bias, and those patients reporting their medication consumption tend to overreport their adherence for various reasons.¹⁰⁹⁻¹¹¹ There is an added complexity associated with the implementation of self-report questionnaires for quality measurement, as they require the need to survey either an entire population, which is likely not feasible, or they require appropriate adjustment to ensure plan representativeness if a random subsample is selected. At a plan level, this would require additional resources that may limit the uptake of the measure and will not provide patient adherence outliers for quality improvement interventions.

Claims data provide a practical approach to adherence calculation for quality reporting and are the current basis for the PQA diabetes metric used in the Medicare Star Ratings adherence calculation. The majority of included studies used a 1-year post-index period as follow-up time, and an adherence quality measure could use a calendar year as measuring period. However, using any of the calculation methods identified in

this SR, pharmacy claims data may not accurately represent the medication supply and currently cannot reflect the appropriate timing and dosing of insulin administration. For this reason, we suggest that, in the long term, consideration is taken to modify database systems used to adjudicate reimbursement. While it is well understood these systems were borne out of a need to track and reimburse insurance claims, they have evolved to serve as research tools and analytical platforms for quality measurement. Allowing pharmacists to enter accurate clinical days supply for products, like insulin, in which there is variation between the reimbursed supply and actual supply available to a patient would enable tracking and reporting of insulin adherence. This tracking and reporting would therefore align the evolution of systems with that of health care, which can only serve to achieve the goal of managing costs while maintaining superior quality of care for the U.S. population.

Role of Quality Measures in U.S. Government Health Care Reform

Currently, the push for improving quality in health care is accelerating in the United States, and this has numerous implications for measuring adherence in diabetes. Plans from the Department of HHS include quality measure initiatives with a focus on improved outcome measures, patient experience measures, and other metrics such as care coordination, access, and delivery. These plans will consider gaps in quality measurement and applicability of measures across health care settings. Currently, CMS considers measures of adherence intermediate outcome metrics—surrogate measures for disease outcomes metrics.¹¹²

Call for an Insulin Quality Measure

Diabetes is one of the diseases targeted as priority by the National Quality Strategy and as such should continue to be a focus of quality measure development.¹¹³ Currently, several quality measures endorsed by NQF for diabetes include adherence measures, but not insulin adherence (Table 1). This gap is important, as a considerable proportion of patients with diabetes, particularly those with advanced disease, use insulin. A quality measure for appropriate use of insulin should therefore be considered.

Because improved disease outcomes (i.e., glycemic control, A1c levels) are considered of highest priority, and patients are the center of care delivery for insulin treatment, a link between outcome and insulin usage would be a relevant target for a quality measure, as it could serve as a gauge to understand the degree to which the health care team is able to partner with patients in improving their health-related engagement and activation. By addressing patient-centric barriers with adherence, specifically with insulin, costs due to microvascular complications may be reduced in the long term. Therefore, patient engagement and education will be essential to help develop

and implement an insulin adherence quality measure. As part of the development process, additional studies confirming the validity of the new measure should be conducted in order to reach consensus.

Conclusions

This SR identifies a range of possible methods to measure adherence to insulin using pharmacy claims or patient-reported questionnaires. We conclude that, while there is some potential based on what has previously been developed, without additional research or modification of current databases used to track claims and measure performance, none of these are currently appropriate for use as a quality measure for insulin adherence. The relevance of insulin adherence as an intermediate outcome for diabetes management is of high priority in the context of health care reform plans with measurable goals. Studies confirming the soundness of new measurement methodology should be conducted.

Authors

SAMUEL STOLPE, PharmD, Pharmacy Quality Alliance, Springfield, Virginia; MICHEL A. KROES, MSc, and NEIL WEBB, BSc Hons, DRG Abacus, Bicester, Oxfordshire, United Kingdom; and TAMI WISNIEWSKI, MPH, Novo Nordisk, Plainsboro, New Jersey.

AUTHOR CORRESPONDENCE: Neil Webb, BSc, DRG Abacus, 6 Talisman Rd., Bicester, Oxfordshire, OX26 6HR, UK. Tel.: 01869 355650; E-mail: nwebb@teamdrg.com

DISCLOSURES

Novo Nordisk paid DRG Abacus to complete the systematic review and manuscript and was involved in the study design, interpretation of data, and decision to publish the findings of the systematic review. Kroes and Webb report personal fees from Novo Nordisk during the conduct of the study and personal fees from DRG Abacus, outside of the submitted work. Webb is employed by DRG Abacus, and Kroes was employed by DRG Abacus at the time of this study. Wisniewski is an employee of Novo Nordisk, which funded the systematic review reported in this article, and also owns stocks in Novo Nordisk. Stolpe has nothing to disclose.

Study concept and design were contributed by Kroes, Webb, and Wisniewski, with assistance from Stolpe. Webb took the lead in data collection, along with Kroes, and data interpretation was performed by all the authors. The manuscript was written by Kroes, Webb, and Wisniewski, with assistance from Stolpe, and revised by Kroes, Stolpe, Wisniewski, and Webb.

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APPENDIX Systematic Review Search Strings

Search Strings Searched November 24, 2014

Embase, 1980 to present		Results
1	exp patient compliance/	103,209
2	exp medication compliance/	5,673
3	(complan* or adheren* or concordan* or persisten*).ti,ab.	559,364
4	or/1-3	609,006
5	exp diabetes mellitus/	608,876
6	exp insulin dependent diabetes mellitus/	80,227
7	insulin dependent diabetes.ti,ab.	22,076
8	T1DM.ti,ab.	4,227
9	(diabetes mellitus and (type 1 or type i or type one)).ti,ab.	19,690
10	(type 1 diabetes or type i diabetes).ti,ab.	40,853
11	exp non insulin dependent diabetes mellitus/	148,504
12	insulin independent diabetes.ti,ab.	133
13	T2DM.ti,ab.	13,970
14	(diabetes mellitus and (type 2 or type ii or type two)).ti,ab.	44,816
15	(type 2 diabetes or type ii diabetes).ti,ab.	107,853
16	NIDDM.ti,ab.	7,737
17	((adult onset or adult-onset) and diabetes).mp.	1,131
18	or/5-17	622,868
19	exp insulin/	242,264
20	insulin*.ti,ab.	337,366
21	exp human insulin/	4,031
22	exp biphasic insulin/	568
23	exp bovine insulin/	702
24	human insulin.mp.	10,147
25	biphasic insulin.mp.	998
26	bovine insulin.mp.	1,252
27	exp short acting insulin/	523
28	short acting insulin.mp.	1,010
29	rapid acting insulin.mp.	787
30	intermediate acting insulin.mp.	291
31	long acting insulin.mp. or exp long acting insulin/	1,888
32	pre-mixed insulin.mp.	54
33	humalog.mp. or exp insulin lispro/	4,115
34	exp insulin aspart/	3,480
35	(novolog or novorapid).mp.	1,085
36	Apidra.mp. or exp insulin glulisine/	1,099
37	Regular humulin.mp.	2
38	novolin.mp.	536
39	Velosulin.mp. or exp neutral insulin/	3,123
40	NPH.mp. or exp isophane insulin/	7,917
41	Lantus.mp. or exp insulin glargine/	6,132
42	Levemir.mp. or exp insulin detemir/	2,414
43	Humulin.mp.	1,606
44	exp insulin degludec/ or degludec.mp.	456
45	tresiba.mp.	25
46	ReliOn.mp.	13
47	exp glucagon like peptide/	14,584
48	(glucagon like peptide or GLP).mp.	17,530
49	exp exendin 4/	6,211
50	exenatide.mp.	2,307
51	Byetta.mp.	790
52	bydureon.mp.	130
53	dulaglutide.mp. or exp dulaglutide/	136
54	trulicity.mp.	2

APPENDIX Systematic Review Search Strings (continued)

Search Strings Searched November 24, 2014

Embase, 1980 to present		Results
55	liraglutide.mp. or exp liraglutide/	3,328
56	(victoza or NN2211).mp.	375
57	lixisenatide.mp. or exp lixisenatide/	357
58	lyxumia.mp.	24
59	albiglutide.mp. or exp albiglutide/	307
60	(eperzan or tanzeum).mp.	8
61	pramlintide.mp. or exp pramlintide/	1,145
62	symlin.mp.	172
63	or/19-62	415,004
64	4 and 18 and 63	8,022
65	exp rheumatoid arthritis/	146,130
66	(arthritis adj2 rheumat*).mp.	163,187
67	(felty* adj2 syndrome).mp.	927
68	(caplan* adj2 syndrome).mp.	126
69	(sjogren* adj2 syndrome).mp.	14,109
70	still* disease.mp.	2,368
71	(spondylitis adj2 ankylosing).mp.	20,873
72	or/65-71	189,589
73	exp disease modifying antirheumatic drug/	7,317
74	(disease modifying antirheumatic drug or DMARD*).mp.	12,466
75	(biologic response modifiers or biologics).mp.	9,297
76	exp recombinant interleukin 1 receptor blocking agent/	4,709
77	(anakinra or kineret).mp.	2,522
78	exp golimumab/	2,396
79	(golimumab or cnto148 or cnto 148 or simponi).mp.	2,459
80	exp adalimumab/	16,255
81	(adalimumab or humira or trudexa).mp.	16,523
82	exp abatacept/	4,511
83	(abatacept or ?rencia or CTLA4 or bms 188667 or bms188667).mp.	7,035
84	exp etanercept/	19,709
85	(etanercept or enbrel or tnr001 or "tnr 001").mp.	20,311
86	exp tocilizumab/	3,692
87	(atlizumab or tocilizumab or actemra or r 1569 or r1569).mp.	4,337
88	exp certolizumab pegol/	2,978
89	((certolizumab adj2 pegol) or cimzia or cdp870 cdp 870 or pha738144 or pha 738144).mp.	3,021
90	or/73-89	50,821
91	4 and 72 and 90	1,622
92	exp multiple sclerosis/	80,941
93	exp acute disseminated encephalomyelitis/	1,097
94	exp myelitis/	49,836
95	(multiple sclerosis or transverse myelitis or optic neuritis or devic or adem or neuromyelitis optica).mp.	95,412
96	'myelo optic neuropathy'.mp. or exp myelo optic neuropathy/	4,095
97	exp demyelinating disease/	109,833
98	or/92-97	159,986
99	exp beta interferon/	17,543
100	(Interferon-beta or Interferon beta).mp.	10,016
101	(beta1a interferon or beta1 interferon).mp.	5,899
102	(avonex or rebif or betaferon or betaseron or extavia or plegridy).mp.	3,596
103	glatiramer.mp. or exp glatiramer/	5,510
104	(cop-1 or cop 1 or copolymer 1 or copaxone).mp.	1,777
105	or/99-104	26,734
106	4 and 98 and 105	854
107	exp Human immunodeficiency virus infection/	303,243
108	exp Human immunodeficiency virus/	137,944

APPENDIX Systematic Review Search Strings (continued)

Search Strings Searched November 24, 2014		
Embase, 1980 to present		Results
109	exp B cell lymphoma/	23,380
110	hiv.ti.ab.	272,593
111	hiv-1.ti.ab.	71,436
112	hiv-2.ti.ab.	4,524
113	human immunodeficiency virus.ti.ab.	74,206
114	human immuno-deficiency virus.ti.ab.	230
115	human immune-deficiency virus.ti.ab.	321
116	acquired immunodeficiency syndrome.ti.ab.	15,093
117	acquired immuno-deficiency syndrome.ti.ab.	110
118	acquired immunodeficiency syndrome.ti.ab.	21
119	acquired immune-deficiency syndrome.ti.ab.	5,301
120	AIDS.mp.	148,631
121	or/107-120	458,143
122	exp Human immunodeficiency virus vaccine/	9,980
123	exp antiretrovirus agent/	140,768
124	exp highly active antiretroviral therapy/	29,942
125	exp Human immunodeficiency virus fusion inhibitor/	9,074
126	exp enfuvirtide/	3,304
127	(enfuvirtide or T-20 or fuzeon).mp.	3,931
128	or/122-126	157,228
129	127 and 128	3,374
130	4 and 121 and 129	449
131	exp human growth hormone/	9,478
132	exp growth hormone/	53,105
133	(human growth hormone or growth hormone or HGH).mp.	79,964
134	(somatropin or somatotropin).mp.	3,050
135	(genotropin or humatrope or norditropin or saizen or omnitrope or nutropin or tev-tropin).mp.	2,247
136	or/131-135	80,279
137	4 and 136	1,943
138	64 or 91 or 106 or 130 or 137	12,740
139	placebo..mp.	324,934
140	double-blind..tw.	144,520
141	139 or 140	370,663
142	138 not 141	11,625
143	limit 142 to yr= "2000 -Current"	9,335
144	limit 143 to english	8,811
145	limit 144 to (adult < 18 to 64 years> or aged < 65+ years>)	3,043
146	animal/ not (human/ and animal/)	1,195,420
147	145 not 146	3,043
MEDLINE In-Process and Other Non-Indexed Citations and Ovid MEDLINE 1946 to Present		Results
1	exp Patient Compliance/	57,988
2	exp Medication Adherence/	8,858
3	(complan* or adheren* or concordan* or persisten*).ti.ab.	45,8742
4	or/1-3	486,054
5	exp Diabetes Mellitus/	330,191
6	exp Diabetes Mellitus, Type 1/	64,055
7	insulin dependent diabetes.mp.	20,211
8	T1DM.mp.	2,214
9	(diabetes mellitus and (type 1 or type i or type one)).ti.ab.	15,022
10	(type 1 diabetes or type i diabetes).ti.ab.	30,354
11	exp Diabetes Mellitus, Type 2/	91,498
12	insulin independent diabetes.ti.ab.	127
13	non insulin dependent diabetes mellitus.ti.ab.	6,862
14	(diabetes mellitus and (type 2 or type ii or type two)).ti.ab.	32,253

APPENDIX Systematic Review Search Strings (continued)

Search Strings Searched November 24, 2014

MEDLINE In-Process and Other Non-Indexed Citations and Ovid MEDLINE 1946 to Present		Results
15	(type 2 diabetes or type ii diabetes).ti,ab.	78,290
16	NIDDM.ti,ab.	6,958
17	((adult onset or adult-onset) and diabetes).mp.	959
18	or/5-17	361,449
19	exp Insulin/	163,699
20	insulin*.ti,ab.	289,561
21	human insulin.mp.	5,418
22	exp Biphasic Insulins/	152
23	biphasic insulin.mp.	563
24	bovine insulin.mp.	799
25	exp Insulin, Short-Acting/	1,210
26	short acting insulin.mp.	385
27	rapid acting insulin.mp.	468
28	intermediate acting insulin.mp.	237
29	long acting insulin.mp. or exp Insulin, Long-Acting/	3,260
30	pre-mixed insulin.mp.	18
31	humalog.mp. or exp Insulin Lispro/	790
32	exp Insulin Aspart/	509
33	(novolog or novorapid).mp.	56
34	apidra.mp.	19
35	regular humulin.mp.	1
36	novolin.mp.	22
37	Velosulin.mp. or exp Insulin, Regular, Pork/	280
38	NPH.mp. or exp Insulin, Isophane/	2,754
39	Lantus.mp.	131
40	levemir.mp.	61
41	Humulin.mp.	126
42	(degludec or tresiba).mp.	136
43	ReliOn.mp.	1
44	exp Glucagon-Like Peptides/	6,058
45	(glucagon like peptide or GLP).mp.	9,955
46	exenatide.mp.	1,963
47	Byetta.mp.	68
48	bydureon.mp.	8
49	(dulaglutide or trulicity).mp.	34
50	liraglutide.mp.	854
51	(victoza or NN2211).mp.	65
52	lixisenatide.mp.	80
53	lyxumia.mp.	8
54	albiglutide.mp.	59
55	(eperzan or tanzeum).mp.	4
56	pramlintide.mp.	488
57	symlin.mp.	19
58	or/19-57	329,607
59	4 and 18 and 58	4,288
60	exp Arthritis, Rheumatoid/	95,813
61	(arthritis adj2 rheumat*).mp.	110,091
62	(felty* adj2 syndrome).mp.	845
63	(caplan* adj2 syndrome).mp.	193
64	(sjogren* adj2 syndrome).mp.	14,002
65	still* disease.mp.	1,848
66	(spondylitis adj2 ankylosing).mp.	14,590
67	or/60-66	134,599
68	exp Antirheumatic Agents/	347,805

APPENDIX Systematic Review Search Strings (continued)

Search Strings Searched November 24, 2014

MEDLINE In-Process and Other Non-Indexed Citations and Ovid MEDLINE 1946 to Present		Results
69	(disease modifying antirheumatic drug or DMARD*).mp.	3,024
70	(biologic response modifiers or biologics).mp.	4,537
71	exp Interleukin 1 Receptor Antagonist Protein/	4,166
72	(anakinra or kineret).mp.	940
73	(golimumab or cnto148 or cnto 148 or simponi).mp.	392
74	exp Immunoconjugates/	8,421
75	(adalimumab or humira or trudexa).mp.	4,116
76	(abatacept or ?rencia or CTLA4 or bms 188667 or bms188667).mp.	5,391
77	(etanercept or enbrel or tnr001 or "tnr 001").mp.	4,659
78	(atlizumab or tocilizumab or actemra or r 1569 or r1569).mp.	1,094
79	((certolizumab adj2 pegol) or cimzia or cdp870 cdp 870 or pha738144 or pha 738144).mp.	464
80	or/68-79	367,102
81	4 and 67 and 80	1,014
82	exp Multiple Sclerosis/	46,516
83	exp Encephalomyelitis, Acute Disseminated/	1,560
84	exp Myelitis, Transverse/	2,457
85	(multiple sclerosis or transverse myelitis or optic neuritis or devic or adem or neuromyelitis optica).mp.	65,814
86	'myelooptic neuropathy'.mp.	2
87	exp Demyelinating Diseases/	81,394
88	or/82-87	96,657
89	exp Interferon-beta/	7,766
90	(Interferon-beta or Interferon beta).mp.	9,803
91	(beta1a interferon or beta1 interferon).mp.	15
92	(avonex or rebif or betaferon or betaseron or extavia or plegridy).mp.	492
93	glatiramer.mp.	1,152
94	(cop-1 or cop 1 or copolymer 1 or copaxone).mp.	1,195
95	or/89-94	10,729
96	4 and 88 and 95	324
97	exp HIV Infections/	246,219
98	exp HIV/	89,074
99	exp HIV-1/	70,894
100	exp HIV-2/	3,944
101	hiv.mp.	292,438
102	hiv-2.mp.	5,593
103	human immunodeficiency virus.ti,ab.	74,287
104	human immunodeficiency virus.ti,ab.	5
105	human immuno-deficiency virus.ti,ab.	204
106	human immune-deficiency virus.ti,ab.	264
107	acquired immunodeficiency syndrome.ti,ab.	15,290
108	acquired immuno-deficiency syndrome.ti,ab.	105
109	acquired immunodeficiency syndrome.ti,ab.	10
110	acquired immune-deficiency syndrome.ti,ab.	5,148
111	exp Acquired Immunodeficiency Syndrome/	75,374
112	AIDS.mp.	166,026
113	or/97-112	386,553
114	exp Anti-HIV Agents/	57,703
115	exp Antiviral Agents/	301,140
116	exp Antiretroviral Therapy, Highly Active/	18,633
117	(enfuvirtide or T-20 or fuzeon).mp.	2,098
118	or/114-116	310,777
119	117 and 118	1,491
120	4 and 113 and 119	121
121	exp Human Growth Hormone/	11,372
122	exp Growth Hormone/	52,066

APPENDIX Systematic Review Search Strings (continued)

Search Strings Searched November 24, 2014

MEDLINE In-Process and Other Non-Indexed Citations and Ovid MEDLINE 1946 to Present		Results
123	(human growth hormone or growth hormone or HGH).mp.	67,449
124	(somatropin or somatotropin).mp.	7,309
125	(genotropin or humatrope or norditropin or saizen or omnitrope or nutropin or tev-tropin).mp.	227
126	or/121-125	68,071
127	4 and 126	1,339
128	59 or 81 or 96 or 120 or 127	7,043
129	randomized controlled trial.pt.	400,323
130	placebo.mp.	169,116
131	or/129-130	476,369
132	128 not 131	6,278
133	limit 132 to yr="2000 -Current"	3,939
134	limit 133 to english	3,656
135	limit 134 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")	1,782
136	animal/ not (human/ and animal/)	4,000,372
137	135 not 136	1,782
The Cochrane Library, including Cochrane Reviews, DARE, HTA, NHS EED		Results
1	exp Patient Compliance/	250
2	exp Medication Adherence/	0
3	(complan* or adheren* or concordan* or persisten*).ti,ab.	868
4	or/1-3	1,059
5	exp Diabetes Mellitus/	1,071
6	exp Diabetes Mellitus, Type 1/	150
7	insulin dependent diabetes.mp.	145
8	T1DM.mp.	9
9	(diabetes mellitus and (type 1 or type i or type one)).ti,ab.	70
10	(type 1 diabetes or type i diabetes).ti,ab.	134
11	exp Diabetes Mellitus, Type 2/	511
12	insulin independent diabetes.ti,ab.	0
13	non insulin dependent diabetes mellitus.ti,ab.	8
14	(diabetes mellitus and (type 2 or type ii or type two)).ti,ab.	287
15	(type 2 diabetes or type ii diabetes).ti,ab.	780
16	NIDDM.ti,ab.	5
17	((adult onset or adult-onset) and diabetes).mp.	19
18	or/5-17	1,704
19	exp Insulin/	185
20	insulin*.ti,ab.	447
21	human insulin.mp.	46
22	exp Biphasic Insulins/	0
23	biphasic insulin.mp.	26
24	bovine insulin.mp.	2
25	exp Insulin, Short-Acting/	0
26	short acting insulin.mp.	21
27	rapid acting insulin.mp.	22
28	intermediate acting insulin.mp.	12
29	long acting insulin.mp. or exp Insulin, Long-Acting/	83
30	pre-mixed insulin.mp.	2
31	humalog.mp. or exp Insulin Lispro/	3
32	exp Insulin Aspart/	0
33	(novolog or novorapid).mp. [mp=ti, ab, tx, kw, ct, hw]	2
34	apidra.mp.	1
35	regular humulin.mp.	1
36	novolin.mp.	2

APPENDIX Systematic Review Search Strings (continued)

Search Strings Searched November 24, 2014

The Cochrane Library, including Cochrane Reviews, DARE, HTA, NHS EED		Results
37	Velosulin.mp. or exp Insulin, Regular, Pork/	187
38	NPH.mp. or exp Insulin, Isophane/	73
39	Lantus.mp.	2
40	levemir.mp.	1
41	Humulin.mp.	5
42	(degludec or tresiba).mp. [mp=ti, ab, tx, kw, ct, hw]	9
43	ReliOn.mp.	0
44	exp Glucagon-Like Peptides/	18
45	(glucagon like peptide or GLP).mp.	79
46	exenatide.mp.	65
47	Byetta.mp.	3
48	bydureon.mp.	0
49	(dulaglutide or trulicity).mp. [mp=ti, ab, tx, kw, ct, hw]	0
50	liraglutide.mp.	42
51	(victoza or NN2211).mp.	2
52	lixisenatide.mp.	5
53	lyxumia.mp.	0
54	albiglutide.mp.	4
55	(eperzan or tanzeum).mp.	0
56	pramlintide.mp.	4
57	symlin.mp.	0
58	or/19-57	591
59	4 and 18 and 58	6
60	exp Arthritis, Rheumatoid/	295
61	(arthritis adj2 rheumat*).mp.	1,100
62	(felty* adj2 syndrome).mp.	32
63	(caplan* adj2 syndrome).mp.	32
64	(sjogren* adj2 syndrome).mp.	58
65	still* disease.mp.	15
66	(spondylitis adj2 ankylosing).mp.	137
67	or/60-66	1,201
68	exp Antirheumatic Agents/	607
69	(disease modifying antirheumatic drug or DMARD*).mp.	161
70	(biologic response modifiers or biologics).mp.	115
71	exp Interleukin 1 Receptor Antagonist Protein/	3
72	(anakinra or kineret).mp.	35
73	(golimumab or cnto148 or cnto 148 or simponi).mp.	41
74	exp Immunoconjugates/	23
75	(adalimumab or humira or trudexa).mp.	213
76	(abatacept or ?rencia or CTLA4 or bms 188667 or bms188667).mp.	61
77	(etanercept or enbrel or tnr001 or "tnr 001").mp.	220
78	(atlizumab or tocilizumab or actemra or r 1569 or r1569).mp.	41
79	((certolizumab adj2 pegol) or cimzia or cdp870 cdp 870 or pha738144 or pha 738144).mp.	24
80	or/68-79	1,012
81	4 and 67 and 80	9
82	exp Multiple Sclerosis/	147
83	exp Encephalomyelitis, Acute Disseminated/	0
84	exp Myelitis, Transverse/	2
85	(multiple sclerosis or transverse myelitis or optic neuritis or devic or adem or neuromyelitis optica).mp.	533
86	'myelo optic neuropathy'.mp.	27
87	exp Demyelinating Diseases/	158
88	or/82-87	543
89	exp Interferon-beta/	47
90	(Interferon-beta or Interferon beta).mp.	114

APPENDIX Systematic Review Search Strings (continued)

Search Strings Searched November 24, 2014		
The Cochrane Library, including Cochrane Reviews, DARE, HTA, NHS EED		Results
91	(beta1a interferon or betal interferon).mp.	0
92	(avonex or rebif or betaferon or betaseron or extavia or plegridy).mp.	23
93	glatiramer.mp.	41
94	(cop-1 or cop 1 or copolymer 1 or copaxone).mp.	10
95	or/89-94	129
96	4 and 88 and 95	3
97	exp HIV Infections/	682
98	exp HIV/	130
99	exp HIV-1/	83
100	exp HIV-2/	3
101	hiv.mp.	2,153
102	hiv-2.mp.	35
103	human immunodeficiency virus.ti,ab.	99
104	human immunodeficiency virus.ti,ab.	0
105	human immuno-deficiency virus.ti,ab.	0
106	human immune-deficiency virus.ti,ab.	0
107	acquired immunodeficiency syndrome.ti,ab.	8
108	acquired immuno-deficiency syndrome.ti,ab.	0
109	acquired immunodeficiency syndrome.ti,ab.	0
110	acquired immune-deficiency syndrome.ti,ab.	2
111	exp Acquired Immunodeficiency Syndrome/	61
112	AIDS.mp.	1,609
113	or/97-112	3,021
114	exp Anti-HIV Agents/	254
115	exp Antiviral Agents/	744
116	exp Antiretroviral Therapy, Highly Active/	109
117	(enfuvirtide or T-20 or fuzeon).mp.	25
118	or/114-116	794
119	117 and 118	14
120	4 and 113 and 119	0
121	exp Human Growth Hormone/	37
122	exp Growth Hormone/	46
123	(human growth hormone or growth hormone or HGH).mp.	188
124	(somatropin or somatotropin).mp.	28
125	(genotropin or humatrope or norditropin or saizen or omnitrope or nutropin or tev-tropin).mp.	16
126	or/121-125	189
127	4 and 126	2
128	59 or 81 or 96 or 120 or 127	20
Update Search Strings Searched June 29, 2015		
Embase 1980 to 2015 Week 26		Results
1	exp patient compliance/	110,331
2	exp medication compliance/	8,768
3	(complian* or adheren* or concordan* or persisten*).ti,ab.	599,798
4	or/1-3	652,123
5	exp diabetes mellitus/	646,611
6	exp insulin dependent diabetes mellitus/	83,898
7	insulin dependent diabetes.ti,ab.	22,256
8	T1DM.ti,ab.	4,650
9	(diabetes mellitus and (type 1 or type i or type one)).ti,ab.	20,862
10	(type 1 diabetes or type i diabetes).ti,ab.	43,673
11	exp non insulin dependent diabetes mellitus/	159,092
12	insulin independent diabetes.ti,ab.	134
13	T2DM.ti,ab.	15,975
14	(diabetes mellitus and (type 2 or type ii or type two)).ti,ab.	49,269

A Systematic Review of Insulin Adherence Measures in Patients with Diabetes

APPENDIX Systematic Review Search Strings (continued)

Update Search Strings Searched June 29, 2015

Embase 1980 to 2015 Week 26		Results
15	(type 2 diabetes or type ii diabetes).ti,ab.	118,106
16	NIDDM.ti,ab.	7,772
17	((adult onset or adult-onset) and diabetes).mp.	1,195
18	or/5-17	663,386
19	exp insulin/	253,199
20	insulin*.ti,ab.	354,613
21	exp human insulin/	4,177
22	exp biphasic insulin/	596
23	exp bovine insulin/	720
24	human insulin.mp.	10,490
25	biphasic insulin.mp.	1,034
26	bovine insulin.mp.	1,280
27	exp short acting insulin/	637
28	short acting insulin.mp.	1,139
29	rapid acting insulin.mp.	827
30	intermediate acting insulin.mp.	306
31	long acting insulin.mp. or exp long acting insulin/	2,050
32	pre-mixed insulin.mp.	59
33	humalog.mp. or exp insulin lispro/	4,270
34	exp insulin aspart/	3,670
35	(novolog or novorapid).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1,134
36	Apidra.mp. or exp insulin glulisine/	1,167
37	Regular humulin.mp.	2
38	novolin.mp.	552
39	Velosulin.mp. or exp neutral insulin/	3,142
40	NPH.mp. or exp isophane insulin/	8,167
41	Lantus.mp. or exp insulin glargine/	6,499
42	Levemir.mp. or exp insulin detemir/	2,572
43	Humulin.mp.	1,645
44	exp insulin degludec/ or degludec.mp.	551
45	tresiba.mp.	41
46	ReliOn.mp.	16
47	or/19-46	425,424
48	4 and 18 and 47	8,348
49	placebo:.mp.	340,182
50	double-blind:.tw.	151,709
51	49 or 50	388,027
52	48 not 51	7,760
53	limit 52 to dd=20141124-20150629	441
54	("Nov* 2014" or "Dec* 2014").dp.	41,333
55	"2015".dp.	59,202
56	54 or 55	100,535
57	52 and 56	57
58	53 or 57	450
59	limit 58 to (english and (adult < 18 to 64 years> or aged <65+ years>))	169
60	animal/ not (human/ and animal/)	1,251,256
61	59 not 60	169
Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1946 to Present		Results
1	exp Patient Compliance/	57,649
2	exp Medication Adherence/	9,326
3	(complan* or adheren* or concordan* or persisten*).ti,ab.	465,434
4	or/1-3	492,430
5	exp Diabetes Mellitus/	330,360

APPENDIX Systematic Review Search Strings (continued)

Update Search Strings Searched June 29, 2015

Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1946 to Present		Results
6	exp Diabetes Mellitus, Type 1/	63,710
7	insulin dependent diabetes.mp.	19,960
8	T1DM.mp.	2,351
9	(diabetes mellitus and (type 1 or type i or type one)).ti,ab.	15,203
10	(type 1 diabetes or type i diabetes).ti,ab.	30,768
11	exp Diabetes Mellitus, Type 2/	92,365
12	insulin independent diabetes.ti,ab.	128
13	non insulin dependent diabetes mellitus.ti,ab.	6,718
14	(diabetes mellitus and (type 2 or type ii or type two)).ti,ab.	33,755
15	(type 2 diabetes or type ii diabetes).ti,ab.	80,905
16	NIDDM.ti,ab.	6,820
17	((adult onset or adult-onset) and diabetes).mp.	943
18	or/5-17	364,040
19	exp Insulin/	161,622
20	insulin*.ti,ab.	289,790
21	human insulin.mp.	5,407
22	exp Biphasic Insulins/	153
23	biphasic insulin.mp.	566
24	bovine insulin.mp.	807
25	exp Insulin, Short-Acting/	1,210
26	short acting insulin.mp.	384
27	rapid acting insulin.mp.	476
28	intermediate acting insulin.mp.	238
29	long acting insulin.mp. or exp Insulin, Long-Acting/	3,290
30	pre-mixed insulin.mp.	21
31	humalog.mp. or exp Insulin Lispro/	796
32	exp Insulin Aspart/	513
33	(novolog or novorapid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	56
34	apidra.mp.	20
35	regular humulin.mp.	1
36	novolin.mp.	21
37	Velosulin.mp. or exp Insulin, Regular, Pork/	277
38	NPH.mp. or exp Insulin, Isophane/	2,751
39	Lantus.mp.	129
40	levemir.mp.	61
41	Humulin.mp.	125
42	(degludec or tresiba).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	167
43	ReliOn.mp.	3
44	or/19-43	323,807
45	4 and 18 and 44	4,276
46	randomized controlled trial.pt.	398,215
47	placebo.mp.	169,137
48	46 or 47	475,470
49	45 not 48	3,809
50	limit 49 to ed=20141124-20150629	111
51	("2014 Nov*" or "2014 Dec*").dp.	138,555
52	2015*.dp.	505,791
53	51 or 52	644,346
54	49 and 53	99
55	50 or 54	175
56	limit 55 to (("all adult (19 plus years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")) and english)	53

APPENDIX Systematic Review Search Strings (continued)

Update Search Strings Searched June 29, 2015

Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1946 to Present		Results
57	animal/ not (human/ and animal/)	3,967,288
58	56 not 57	53
CDSR, DARE, CLHTA, CLEED		Results
1	exp Patient Compliance/	253
2	exp Medication Adherence/	0
3	(complan* or adheren* or concordan* or persisten*).ti,ab.	932
4	or/1-3	1,125
5	exp Diabetes Mellitus/	1,133
6	exp Diabetes Mellitus, Type 1/	157
7	insulin dependent diabetes.mp.	143
8	T1DM.mp.	10
9	(diabetes mellitus and (type 1 or type i or type one)).ti,ab.	75
10	(type 1 diabetes or type i diabetes).ti,ab.	147
11	exp Diabetes Mellitus, Type 2/	539
12	insulin independent diabetes.ti,ab.	0
13	non insulin dependent diabetes mellitus.ti,ab.	8
14	(diabetes mellitus and (type 2 or type ii or type two)).ti,ab.	324
15	(type 2 diabetes or type ii diabetes).ti,ab.	860
16	NIDDM.ti,ab.	5
17	((adult onset or adult-onset) and diabetes).mp.	18
18	or/5-17	1,834
19	exp Insulin/	197
20	insulin*.ti,ab.	478
21	human insulin.mp.	47
22	exp Biphasic Insulins/	0
23	biphasic insulin.mp.	29
24	bovine insulin.mp.	2
25	exp Insulin, Short-Acting/	0
26	short acting insulin.mp.	21
27	rapid acting insulin.mp.	22
28	intermediate acting insulin.mp.	13
29	long acting insulin.mp. or exp Insulin, Long-Acting/	87
30	pre-mixed insulin.mp.	2
31	humalog.mp. or exp Insulin Lispro/	3
32	exp Insulin Aspart/	0
33	(novolog or novorapid).mp. [mp=ti, ab, tx, kw, ct, hw]	2
34	apidra.mp.	1
35	regular humulin.mp.	1
36	novolin.mp.	2
37	Velosulin.mp. or exp Insulin, Regular, Pork/	199
38	NPH.mp. or exp Insulin, Isophane/	73
39	Lantus.mp.	2
40	levemir.mp.	1
41	Humulin.mp.	5
42	(degludec or tresiba).mp. [mp=ti, ab, tx, kw, ct, hw]	11
43	ReliOn.mp.	0
44	or/19-43	538
45	4 and 18 and 44	6
46	limit 45 to yr="2014 -Current" [Limit not valid in DARE; records were retained]	0