

## Evidence-based Practice Center Systematic Review Protocol

### Project Title: Closing the Quality Gap Series: Comparative Effectiveness of Medication Adherence Interventions

Amendment Date(s) if applicable:  
(Amendments Details—see Section VII)

#### I. Background and Objectives for the Systematic Review

##### A. Overview and Fit With Goals of AHRQ's Closing the Quality Gap Initiative

To achieve the goals of quantitatively improving the quality and effectiveness of health care for all Americans, knowledge and tools are needed. Although medical researchers have demonstrated many efficacious medical treatments to improve health outcomes, a recent report by the Institute of Medicine identified a disquieting discrepancy between present treatment success rates and those thought to be achievable.<sup>1</sup> This gap has partly been attributed to barriers that providers face in implementing best practice guidelines.<sup>1,2</sup> Patients' adherence to recommended treatment, however, provides an additional explanation for the incongruity between recommended treatment and actual treatment outcomes. Medication adherence in particular is defined as "the extent to which patients take medication as prescribed by their health care providers."<sup>3 (p. 487)</sup> In the same sense that health outcomes may be improved by enhancing provider implementation of best practice guidelines, they may also be improved by helping patients to better adhere to recommended treatment.<sup>4-6</sup>

Over the past half century, rapid advances have been made in the pharmacological management of many acute and chronic health problems, including diabetes, tuberculosis, HIV/AIDS, hypertension, hypercholesterolemia, and cardiovascular disease. When left untreated or undertreated, particularly in the setting of chronic illness,<sup>7</sup> these conditions often lead to complications (e.g., myocardial infarction, stroke, kidney failure, immune compromise) that decrease patients' quality of life and increase their risk of death.<sup>8</sup> Despite the established capacity for many medications to reduce both mortality and morbidity, many patients do not use their medications as recommended by health care providers.<sup>3,5,8-10</sup> Although the specific consequences of suboptimal adherence to medications are quite variable, depending on the condition treated and the prescribed treatment, poor adherence clearly poses a threat to the health of the U.S. population<sup>10,11</sup> that must be addressed to reduce the gap between potential and actual health care quality. Moreover, researchers have suggested that factors that affect adherence differ, depending on the chronicity of the illness.<sup>7,12,13</sup> Glasgow and colleagues<sup>7</sup> have suggested that, as a result, chronic illness cannot be addressed adequately with a traditional, directive acute care model that is appropriate for acute illness. Instead, support of adherence to treatment of chronic illness, they purport, requires active engagement of patients in their treatment over time, hence using a newer chronic care model.

Moreover, as described below in the section discussing health disparities, medication adherence is particularly salient for a number of vulnerable populations of interest to the Agency for Healthcare Research and Quality (AHRQ) and the Institute of Medicine, including ethnic minorities, people with low literacy, and the elderly. Thus, understanding approaches to enhancing medication adherence may provide a way to reduce health disparities.

Because medication adherence is becoming more recognized as an important health care–quality issue, treatment guidelines often include recommendations for providers to consider adherence. Currently, available guidelines and recommendations that address issues related to medication adherence are predominantly disease specific and focused on a particular condition, such as HIV/AIDS, tuberculosis, asthma, overweight/obesity, and mental health. Furthermore, adherence is not the focus of these guidelines, but rather one among several issues discussed in the area of disease treatment and management. Recent disease-specific recommendations include those published by the U.S. Department of Veterans Affairs and the New York State Department of Health. Guidelines authored by the National Collaborating Centre for Primary Care on behalf of the United Kingdom-based National Institute for Health

and Clinical Excellence provide recommendations pertaining to medication adherence that are not disease specific.<sup>14-18</sup> Details regarding these guidelines are shown in Table 1.

**Table 1. Guidelines for medication adherence**

Title	Source	Date
Medicines Adherence: Involving Patients in Decisions About Prescribed Medicines and Supporting Adherence <sup>17</sup>	Developed by the National Collaborating Centre for Primary Care in behalf of the National Institute for Health and Clinical Excellence (United Kingdom)	2009
VA/DoD Clinical Practice Guideline for Management of Asthma in Children and Adults <sup>15</sup>	U.S. Department of Veterans Affairs/ U.S. Department of Defense	2009
VA/DoD Clinical Practice Guideline for Screening and Management of Overweight and Obesity <sup>16</sup>	U.S. Department of Veterans Affairs/ U.S. Department of Defense	2006
VA/DoD Clinical Practice Guideline for Management of Major Depressive Disorder <sup>14</sup>	U.S. Department of Veterans Affairs/ U.S. Department of Defense	2009
Adherence to Antiretroviral Therapy Among HIV-Infected Patients With Mental Health Disorders <sup>18</sup>	New York State Department of Health	2006

## B. Burden, Scope, and Prevalence of the Problem

As described in this section, poor adherence is very common.<sup>3,10</sup> Studies have shown consistently that 20 to 30 percent of medication prescriptions are never filled and that up to 50 percent are not taken as prescribed.<sup>11</sup> Across the many studies that have been conducted to estimate the prevalence of medication nonadherence, DiMatteo and colleagues<sup>8</sup> estimated that 21 percent of patients do not take their medications as recommended. Further, nonadherence tends to occur with greater frequency when the medications are used to treat asymptomatic, chronic conditions such as hypertension and hypercholesterolemia. The literature suggests that 20 to 75 percent of patients who are prescribed medications for these conditions are not adhering to the regimen at their 1-year followup.<sup>3,9</sup> This lack of adherence to medical advice has been estimated to cause approximately 125,000 deaths, at least 10 percent of hospital admissions,<sup>11</sup> and substantial worsening of morbidity and mortality.<sup>8,19</sup> Moreover, nonadherence has been estimated to cost the U.S. health care system \$100 billion annually in direct costs.<sup>11</sup>

Observational studies focusing on the factors that cause medication nonadherence have shown that it is a complex behavior with multiple determinants. Taking medication to improve health outcomes requires both a functioning health care *system* and appropriate *individual behaviors*. Thus, both system and individual factors can lead to nonadherence. Assuming a patient has access to a health care provider who prescribes an appropriate medication, at the correct dose, and for the correct duration, *system* factors related to nonadherence include a lack of ability to purchase the initial prescription or refills; inadequate instructions given for taking the medication; insufficient labeling of the medication container to promote correct adherence; inadequate information given about the benefits and risks of and alternatives to the prescribed medication; and lack of access to a provider who will monitor the response to medication and change the dosage or medication type accordingly. Many health care systems operate on an acute care model that fails to engage patients in their own care and thus serves as a barrier to promoting adherence to chronic illness treatment that requires such engagement.<sup>7</sup> Hence, understanding ways to overcome such barriers at the system level is particularly important in the setting of long-term treatment for chronic diseases.

Likewise, many *individual factors* underlie nonadherence. For example, patients may lack the cognitive ability to understand the need for the medication or how to take it. Others may not feel motivated to take

the medication or may lack the skills and resources that support adherence.<sup>20-22</sup> Substance abuse, depression,<sup>5,20,23,24</sup> lack of medical insurance, competing demands on time, and having an erratic daily routine have been shown to get in the way of taking medications optimally.<sup>10,20</sup> Moreover, the factors that most influence adherence vary by individual.<sup>20</sup> Therefore, interventions to improve adherence are often multipronged and tailored. Of note, the cognitive barriers that patients with psychosis and mania face in taking medication likely differ from those that are associated with other chronic conditions; hence, we would like to exclude psychosis and mania from our review. In addition, the ways in which patients may be nonadherent are many. For example, some patients may omit doses of a medication, whereas others may take extra doses. Also, they may take the wrong amount of the medication—either too little or too much—or take the medication at the wrong time of day. Patients can also be nonadherent simply by not following instructions on how to take the medication (e.g., with or without food). Also, they may take drug holidays, whereby they discontinue the medication for a period of time or even discontinue the medication altogether.

Many studies have examined the multiple factors associated with medication adherence. Bosworth<sup>21</sup> classified these factors into five categories (the first two generally considered *system* factors, and the others generally considered *individual* factors): policy and healthcare systems, the social environment, individual provider characteristics, regimen characteristics, and patient characteristics.

### C. Means To Address the Problem

To improve health care quality, interventions used to improve medication adherence have been developed that address individual or system factors. Previous reviews of the interventions that have been developed and tested demonstrate considerable variability, in terms of both approach and effectiveness.<sup>4,25</sup> In a recently published meta-analysis of 61 trials of individual-level programs to improve medication adherence,<sup>11</sup> the effect size for improved adherence in the behavioral cohorts (the only ones meeting homogeneity criteria) was 7 percent (95% confidence interval [CI], 4% to 9%); for educational interventions, 11 percent (95% CI, 6% to 15%); and for combined interventions, 8 percent (95% CI, 4% to 12%). Though most adherence-intervention trials have demonstrated only modest improvement, a recent trial of a pharmacy care program reported substantial improvement in adherence, suggesting it will be important to assess not only individual but also structure-level interventions.<sup>26</sup>

Although it is possible to develop programs to improve medication adherence, questions about the types of programs most likely to be effective in various settings remain unanswered. For example, reviews of other behavioral interventions have shown that those developed to address specific constructs based on a specific behavioral theory are more effective than those that were not;<sup>27</sup> however, this feature has not been compared for medication adherence<sup>28</sup> or across diseases. The last comprehensive high-quality review on this topic was a 2008 update of a Cochrane review, which found that “several quite simple interventions increased adherence and improved patient outcomes, but the effects were inconsistent from study to study with less than half of studies showing benefits.”<sup>4(p. 2)</sup> The authors, however, analyzed the results by clinical condition rather than by the type of intervention, vulnerable subpopulations, methods used to assess adherence, purpose of medication (primary, secondary, or tertiary prevention), or disease-specific measures (severity/stage of disease), all of which would provide more guidance for strategies to improve health care quality. Patterns of adherence and factors influencing it have been shown to differ for acute disease when compared with chronic disease,<sup>12</sup> likely because of the longer duration of medication taking required with chronic disease. For this reason, and because their longer duration means chronic diseases cause greater disease burden, our review will focus on adherence to medication for chronic illness to maintain comparability across intervention types. Moreover, the previous review did not assess the impact of system-level interventions on adherence.<sup>4</sup> Thus, in our review, we would like to assess these interventions and those at the patient and provider levels. Because recent reviews and meta-analyses have assessed the impact of interventions to improve medication adherence

in the context of HIV treatment,<sup>28-30</sup> we will exclude antiretroviral adherence intervention studies from our review.

#### D. Health Disparities

Studies demonstrate that health disparities exist for many common chronic diseases, including cardiovascular disease, diabetes mellitus, hypertension, HIV infection, and depression. However, the extent to which these differences are due to medication adherence is unclear. Studies have shown ethnic differences in medication-adherence rates that may partly explain observed health disparities.<sup>22,31,32</sup> For example, multiple studies have documented that African Americans are less adherent to antiretroviral treatment than whites and have postulated that this may explain differences in clinical outcomes.<sup>21,22,31,32</sup> Although the reasons for these differences in adherence are not fully understood, phenomena such as less trust in the health care system have been suggested. Similarly, poor adherence has been identified as particularly problematic for older adults, who often must take multiple medications in the face of physical and cognitive limitations.<sup>33</sup>

Low health literacy may also be linked to poor adherence and poor health outcomes. Health literacy is defined in Healthy People 2010 as the degree to which individuals can obtain, process, and understand the basic health information and services they need to make appropriate health decisions.<sup>34</sup> In a systematic review of 44 studies that examined the relationship between health literacy and health outcomes, 16 examined the association between health literacy and knowledge.<sup>35</sup> Health literacy was associated with greater knowledge in 14 of the 16 studies reviewed, including studies that examined patient knowledge of diabetes, hypertension, and heart health.<sup>36,37</sup> Low literacy has also been associated with greater risk of hospitalization<sup>38,39</sup> and poorer control of type 2 diabetes.<sup>36,40-42</sup>

Only a handful of studies have examined the association between health literacy and medication adherence, however, and the results of these studies have been conflicting. Whereas Kalichman and colleagues found low literacy to be associated with poorer compliance with highly active antiretroviral therapy among HIV-infected patients,<sup>43</sup> other studies have failed to replicate this finding.<sup>20,44</sup> Nonetheless, other studies demonstrate that patients with low literacy skills have difficulty understanding prescription warning labels and identifying their medications correctly.<sup>45,46</sup> Thus, patients with limited literacy skills may be at greater risk than others for medication misadministration.

#### E. Summary and Objectives

To address the issues outlined above, the overarching goal of our systematic review is to maximize the quality of care for adults with chronic disease by seeking to identify individual- and system-level interventions that have been shown to improve medication adherence and to better understand the key components of effective interventions and how intervention effectiveness varies for vulnerable subpopulations (such as racial and ethnic minorities, low-health literacy groups, the elderly, and so on). Recent meta-analyses and reviews of HIV medication adherence interventions have been conducted. As a result, to avoid duplication, we will not include studies of interventions to improve adherence to antiretroviral treatment. Moreover, because severe mental illness adds a layer of complexity to the cognitive features of medication adherence that make it less generalizable across other diseases, we will not include studies of medication adherence interventions for schizophrenia, bipolar disorder, or substance abuse.

## II. Key Questions

### Question 1

- a. Among patients with chronic diseases with self-administered medication prescribed by a provider, what is the comparative effectiveness of interventions aimed at patients, providers, systems, and combinations of audiences in improving medication adherence?

b. Is improved medication adherence associated with improvement in patient outcomes?

### Question 2

a. Among patients with chronic diseases with self-administered medication prescribed by a provider, what is the comparative effectiveness of policy interventions in improving medication adherence?

b. Is improved medication adherence associated with improvement in patient outcomes?

### Question 3

How do medication-adherence intervention characteristics (e.g., mode of delivery, intervention target, intensity) vary? To what extent do the effects of adherence interventions vary based upon their characteristics?

### Question 4

To what extent do the effects of adherence interventions vary based on differences in vulnerable subpopulations?

### Question 5

What unintended consequences are associated with interventions to improve medication adherence?

The Key Questions (KQs) for the proposed review were posted for public comment for 4 weeks on the Effective Health Care Program Web site, and input was obtained from a Technical Expert Panel (TEP). Based on this input the KQs and scope were clarified primarily for readability and greater comprehensiveness. We also modified KQ 2 to focus solely on systems-level interventions to reflect feedback from preliminary analysis, the TEP, and public comments that policy interventions would be difficult to separate from patient- or provider-level interventions (all now included within KQ 1).

### PICOTS Criteria for the Key Questions

- **Population(s)**

Patients who are prescribed self-administered medications for single or multiple chronic diseases. Vulnerable subpopulations of interest may include but are not limited to racial and ethnic minorities; populations with special health care needs (such as low health literacy, comorbid disease, or severe disease); the elderly; and low-income, underinsured, uninsured, and inner-city or rural populations. Relevant medications include all medications prescribed by a provider, including over-the-counter drugs. We will not review studies of populations with acute illness, substance abuse, or psychotic illness to maintain comparability with interventions relevant for chronic illness. We are also excluding HIV studies because they have been the subject of past and ongoing reviews.

- **Interventions**

1. Any intervention intended to improve adherence with prescribed, self-administered medications. Examples include:
  - a. Patient education
  - b. Face-to-face or telephone counseling or therapy (individual, couple, family, or group)
  - c. Behavioral interventions
  - d. Case management
  - e. Simplified dosing
  - f. Reminders

- g. System changes
- h. Changes to medication formulations
- i. Augmented pharmacy services
- j. Shared decisionmaking
- k. Dose-dispensing units of medication or medication charts
- l. Rewards
- m. Directly observed therapy (DOT) or modified DOT

Any intervention intended to address policy barriers. Examples include changes in copay and refill practices (e.g., how long medications are prescribed for, how often patients have to order refills) and changes in formularies. Characteristics of the intervention that may influence effectiveness include but are not limited to the following:

- a. Target of the intervention
- b. Agent delivering the intervention (e.g., physician, nurse, or health educator) and his/her characteristics/level of training
- c. Intensity (contact time)
- d. Duration (number of sessions over a given time period)
- e. Delivery mode (e.g., face-to-face, written material, text message, computer, over-the-phone)
- f. Role of theory
- g. Number of components
- h. Type of components (based on the taxonomy proposed by de Bruin and colleagues<sup>47</sup>):
  - (1). Knowledge-based (general information about behavior-related health consequences, use of individualized information, increase in understanding/memory enhancement)
  - (2). Awareness-based (risk communication, self-monitoring, reflective listening, behavioral feedback)
  - (3). Social influence (information about peers or social influence of peers)
  - (4). Attitude-based
  - (5). Self-efficacy (modeling, practice, verbal persuasion, coping responses, graded tasks, reattribution of success/failure)
  - (6). Intention formation (general intention, medication schedule, goals, behavioral contract)
  - (7). Action control (cues/reminders, self-persuasion, social support)
  - (8). Maintenance (maintenance goals, relapse prevention)
  - (9). Facilitation (continuous professional support, dealing with adverse effects, individualizing/simplifying regimen [fewer pills, fewer medications, less frequent dosing, timing of dosing to fit individual schedule], reducing environmental barriers)
  - (10). Contingent rewards
  - (11). Motivational interviewing
  - (12). Stress management

The specific medications will vary by clinical condition.

- **Comparators**

Usual or routine care, defined as the absence of intervention to improve medication adherence or comparison among interventions.

- **Outcomes Measures**

1. Medication adherence
2. Other outcomes
  - a. Biomarkers of clinical outcomes
  - b. Clinical outcomes (mortality, morbidity measures defined by the clinical condition)

- c. Quality of life
- d. Patient satisfaction
- e. Health care utilization (including associated costs)
- f. Quality of care

3. Adverse events

- **Timing**

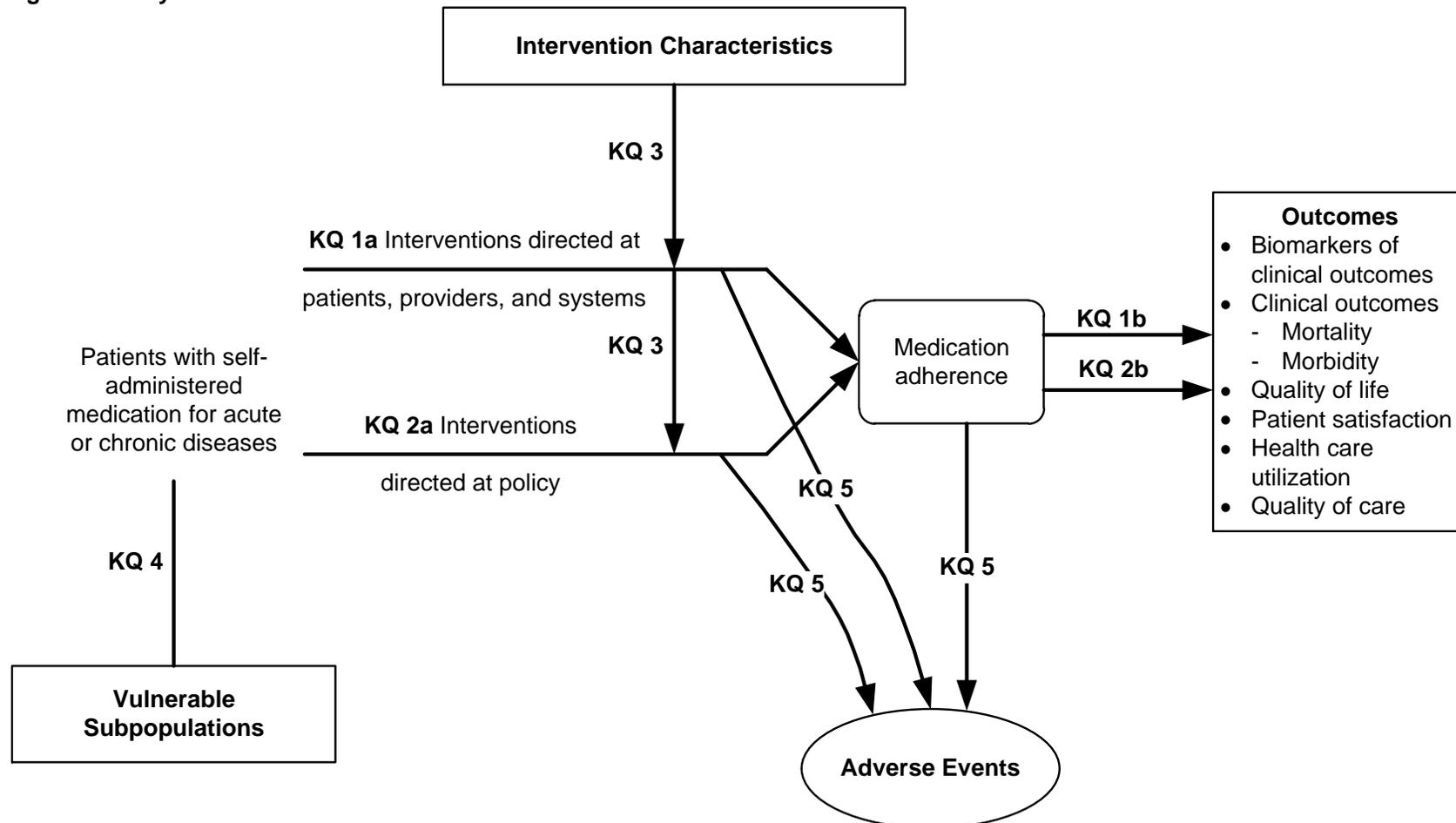
All timing

- **Settings**

Outpatient primary and specialty care settings will be included. Institutional settings such as inpatient care, nursing homes, and prisons will be excluded. Non-U.S. studies will be excluded; studies conducted in other settings may be of limited applicability in the United States.

### III. Analytic Framework

Figure 1. Analytic framework for medication adherence



The analytical framework depicts the Key Questions (KQs) within the context of the populations, interventions, comparators, outcomes, timing, and settings (PICOTS) framework described in the previous section. In general, the figure illustrates how patients with self-administered medications for chronic disease may be given interventions to improve medication adherence and other outcomes. These interventions may be directed at patients, providers, or policymakers (KQ 1) or at health systems (KQ 2). KQ 1a and KQ 2a evaluate the effect of interventions on medication adherence. Changes in medication adherence may be followed by changes in intermediate outcomes, such as biomarkers, or in other health outcomes, such as morbidity and mortality, health care utilization, and quality of life (KQ 1b and KQ 2b). KQ3 examines whether the effectiveness of these interventions is influenced by characteristics of the intervention. KQ 4 explores the effectiveness of interventions to improve medication adherence and other outcomes for vulnerable subpopulations. These interventions may have unanticipated consequences (KQ 5).

#### IV. Methods

##### A. Criteria for Inclusion/Exclusion of Studies in the Review.

Table 2 presents the inclusion/exclusion criteria for our review. We do not repeat all of the information on populations, interventions, comparators, outcomes, timing, settings (PICOTS) related to inclusion/exclusion criteria.

**Table 2. Inclusion/exclusion criteria**

Category	Criteria	
	Inclusion	Exclusion
Population	<ul style="list-style-type: none"> <li>Adults prescribed self-administered medication for secondary or tertiary prevention of chronic diseases</li> </ul>	<ul style="list-style-type: none"> <li>Children under the age of 18 (no adults in the study or outcome of interest not stratified by child/adult)</li> <li>Patients administered medications in hospitals or in offices</li> <li>Patients undergoing primary prevention</li> <li>Patients taking over-the-counter medicines not prescribed by a provider</li> <li>Patients with infectious conditions (e.g., HIV, tuberculosis, pelvic inflammatory disease)</li> <li>Patients with mental illness involving psychosis or mania</li> <li>Patients on medication to treat substance abuse</li> </ul>
Geography	<ul style="list-style-type: none"> <li>United States</li> </ul>	<ul style="list-style-type: none"> <li>All non-United States</li> </ul>
Time period	<ul style="list-style-type: none"> <li>1994 to present; searches to be updated after draft report goes out for peer review</li> </ul>	<ul style="list-style-type: none"> <li>Pre-1994</li> </ul>
Length of followup	<ul style="list-style-type: none"> <li>No limit</li> </ul>	
Settings	<ul style="list-style-type: none"> <li>Outpatient primary and specialty care settings</li> </ul>	<ul style="list-style-type: none"> <li>Institutional settings (e.g., inpatient care, nursing homes, prisons)</li> </ul>

Category	Criteria	
	Inclusion	Exclusion
Interventions	<ul style="list-style-type: none"> <li>Any intervention (other than for populations with acute disease, substance abuse, psychotic illness, or HIV infection) intended to improve adherence with prescribed, self-administered medications</li> </ul>	<ul style="list-style-type: none"> <li>Interventions intended to improve compliance with primary prevention measures (e.g., screening, diet, exercise, lifestyle changes)</li> </ul>
Outcomes	<ul style="list-style-type: none"> <li>Medication adherence</li> <li>Biomarkers, mortality, morbidity, quality of life, patient satisfaction, and health utilization (and associated costs) for studies with a significant improvement in medication adherence</li> <li>Adverse events</li> </ul>	
Publication language	<ul style="list-style-type: none"> <li>English</li> </ul>	<ul style="list-style-type: none"> <li>All other languages (due to limited applicability)</li> </ul>
Admissible evidence for KQ 1 on patient-level, provider-level, or policy-level interventions (study design and other criteria)	<ul style="list-style-type: none"> <li>Original research; eligible study designs include:               <ul style="list-style-type: none"> <li>Randomized controlled trials</li> <li>Systematic reviews with or without meta-analyses</li> </ul> </li> <li>We will include systematic reviews and controlled trials for all outcomes. Results from high-quality recent review may be used within the review if their criteria are consistent with the criteria for our review.</li> </ul>	<ul style="list-style-type: none"> <li>Nonrandomized controlled trials</li> <li>Observational study designs</li> <li>Case series</li> <li>Case reports</li> <li>Nonsystematic reviews</li> <li>Editorials</li> <li>Letters to the editor</li> <li>Articles rated poor during quality assessment</li> <li>Studies with historical, rather than concurrent, control groups</li> <li>N &lt; 40</li> </ul>
Admissible evidence for system-level interventions (study design and other criteria)	<ul style="list-style-type: none"> <li>Original research; eligible study designs include:               <ul style="list-style-type: none"> <li>Randomized controlled trials</li> <li>Systematic reviews with or without meta-analyses</li> <li>Nonrandomized controlled trials</li> <li>Cohort studies</li> <li>Case-control studies</li> <li>Time series</li> <li>Before-after studies</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional studies</li> <li>Case series</li> <li>Case reports</li> <li>Nonsystematic reviews</li> <li>Editorials</li> <li>Letters to the editor</li> <li>Articles rated poor in quality during assessment</li> <li>N &lt; 40</li> </ul>

## B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

We will systematically search, review, and analyze the scientific evidence for each KQ. The steps that we will take to accomplish the literature review are described below.

To identify articles relevant to each KQ, we will begin with a focused MEDLINE® search for medication adherence interventions using a combination of MeSH® and title and abstract keywords (Table 3). We will also search the Cochrane Library and the Cochrane Central Trials Registry using analogous search terms. To identify articles specifically relevant to KQ 2, we will conduct a second, “policy-oriented” search (Table 4) and will add unique results to those references identified in the main search for medication adherence interventions.

**Table 3. Initial literature search terms for interventions used to improve medication adherence**

<b>Population</b>	<b>"Patient Compliance"[MeSH] OR "Patient Compliance"[ti] OR "Medication Adherence"[MeSH] OR adherence[tiab]</b>
Interventions	"Intervention Studies"[MeSH] OR intervention[tiab]
Limits	Humans English All Adult: 19+ years Publication Date from 1994 RCT Not: Editorial, Letter, Comment, News

**Table 4. Initial literature search terms for policy-oriented interventions used to improve medication adherence**

<b>Population</b>	<b>"Patient Compliance"[MeSH] OR "Patient Compliance"[ti] OR "Medication Adherence"[MeSH] OR adherence[tiab]</b>
Interventions	We will use multiple search terms to capture policy-oriented interventions (e.g., insurance-based, formulary-based, or access-based). The specific search strategy will include the following:  "Intervention Studies"[MeSH] OR intervention[tiab] AND "Policy Making"[MeSH] OR "Public Policy"[MeSH] OR "State Health Planning and Development Agencies"[MeSH] OR "Insurance Claim Review"[MeSH] OR "Medicare Part D"[MeSH] OR "Health Services Accessibility"[MeSH] OR "Health Policy"[MeSH] OR "Formularies as Topic"[MeSH] OR "Gatekeeping"[MeSH] OR "Community Pharmacy Services"[MeSH] OR "Medication Therapy Management"[MeSH] OR "Cost-Sharing"[MeSH] OR "cost sharing" OR "Health Benefit Plans, Employee"[MeSH] OR "prior authorization" OR "Insurance, Pharmaceutical Services"[MeSH] OR "Prescription Drugs"[MeSH] OR "Drug Costs"[MeSH] OR "system-level" OR "pharmaceutical care program" OR "pharmaceutical care programs" OR "Health Services Research"[MeSH] OR "Medical Indigency"[MeSH] OR "Program Development"[MeSH] OR "medication possession ratio" OR "medication possession ratios" OR MPR OR "Pharmacy Service, Hospital"[MeSH] OR "prescribing pattern" OR "prescribing patterns" OR "Medicaid"[MeSH] OR "Treatment Refusal"[MeSH] OR "Polypharmacy"[MeSH] OR "Drug Combinations"[MeSH] OR "Drug Packaging"[MeSH] OR "Disease Management"[MeSH] OR "Drug Administration Schedule"[MeSH] OR "Managed Care Programs"[MeSH] OR "Health Maintenance Organizations/organization and administration"[MeSH] OR "Primary Health Care/economics"[MeSH] OR "Primary Health Care/organization and administration"[MeSH]
Limits	Humans English All Adult: 19+ years Publication Date from 1994

Should we fail to find published studies on known interventions, we will search the grey literature for unpublished studies relevant to our review and will include studies that meet all inclusion criteria and contain enough methodological information to permit us to assess internal validity/quality. Potential sources of grey literature include ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform, and Health Services Research Projects in Progress.

We reviewed our search strategy with the TEP and supplemented it as needed according to their recommendations. In addition, to avoid retrieval bias, we will manually search the reference lists of landmark studies and background articles on medication adherence to look for any relevant citations that might have been missed by electronic database searches.

We will also conduct an updated literature search (of the same databases searched initially) concurrent with the peer review process. Any literature suggested by peer reviewers or from the public will be investigated and, if appropriate, incorporated into the final review. Appropriateness will be determined by the same methods listed above.

### **C. Data Abstraction and Data Management**

All titles and abstracts identified through searches will be independently reviewed for eligibility against our inclusion/exclusion criteria by two trained members of the research team. Studies marked for possible inclusion by either reviewer will undergo a full-text review. For studies that lack adequate information to determine inclusion or exclusion, we will retrieve the full text and then make the determination. All results will be tracked in an EndNote® database.

We will retrieve and review the full text of all titles included during the title/abstract review phase. Each full-text article will be independently reviewed by two trained members of the team for inclusion or exclusion based on the eligibility criteria described above. If both reviewers agree that a study does not meet the eligibility criteria, the study will be excluded. If the reviewers disagree, conflicts will be resolved by discussion and consensus or by consulting a third member of the review team. As described above, all results will be tracked in an EndNote database. We will record the reason why each excluded full-text publication did not satisfy the eligibility criteria so that we can later compile a comprehensive list of such studies.

For studies that meet our inclusion criteria, we will abstract important information into evidence tables. As implied by KQ 1 and KQ 2, we will synthesize evidence on other outcomes only for interventions that show improvement in medication adherence. We will use thresholds for medication adherence as defined by each study, that is, we will not predefine standards for improvement in medication adherence for all clinical conditions. We will limit the abstraction of morbidity data to primary or secondary outcomes as defined by the study. If studies fail to define primary or secondary outcomes, we will collect all outcomes. To test the feasibility of this approach, we will test the approach with a sample of studies. We will design data abstraction forms to gather pertinent information from each article, including the characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. We will abstract information on patient characteristics such as age, sex, race/ethnicity, special health care needs (such as low–health literacy groups, comorbid disease, or severe disease), income, insurance status, and geographic location (inner city or rural). We will also abstract intervention characteristics as described in KQ 3. Trained reviewers will extract the relevant data from each included article into the evidence tables. All data abstractions will be reviewed for completeness and accuracy by a second member of the team.

### **D. Assessment of Methodological Quality of Individual Studies.**

To assess the quality (internal validity) of studies, we will use predefined criteria based on those developed by AHRQ.<sup>48</sup> In general terms, a “good” study has the least risk of bias, and its results are considered to be valid. A “fair” study is susceptible to some risk of bias but probably not enough to invalidate its results. A “poor” study has significant risk of bias (e.g., stemming from serious errors in design or analysis) that may invalidate its results. Specific concerns for our review include selection bias and detection bias. For selection bias, we will evaluate studies for their approach to accounting or controlling for variations in past nonadherent behavior. We will also evaluate whether the intervention measured or accounted for any skills necessary to be adherent. We will also evaluate whether studies vary by intervention arms on confounders and effect modifiers such as other prescription drugs, dose/frequency of medication, length of time since diagnosis, and length of time on the prescription medication. For detection bias, we will evaluate the method of recording adherence. For studies that go

beyond medication adherence to mediator analysis of outcomes, we will evaluate the validity of thresholds separating adherence from nonadherence. Two independent reviewers will assign quality ratings for each study. Disagreements between the two reviewers will be resolved by discussion and consensus or by consulting a third member of the team.

## E. Data Synthesis

KQs 1, 2, and 3 will present results categorized by clinical condition. KQ 4 will present results categorized by intervention characteristics. We specified all nonmorbidity data a priori and listed them above in the PICOTS criteria. Because of the breadth of the topic for our review, we have elected, based on feedback from our TEP, to collect a comprehensive set of morbidity outcomes (and their biomarkers) rather than make a priori judgments about which morbidity outcomes to include. We will evaluate the poolability of collected morbidity data. If we find three or more similar studies for a comparison of interest, we will consider quantitative analysis (i.e., meta-analysis) of the data from those studies.

To determine whether quantitative analyses are appropriate, we will assess the heterogeneity of the studies under consideration. When quantitative analyses are not appropriate (e.g., because of heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we will synthesize the data qualitatively. We anticipate that much of the data found in our review will be synthesized qualitatively.

We plan to stratify analyses and perform subgroup analyses when possible and appropriate. Planned stratifications or categories for subgroup analyses include disease type, intervention characteristics, racial and ethnic minorities, low–health literacy groups, and the elderly.

## F. Grading the Evidence for Each Key Question.

We will grade the strength of evidence based on the guidance established by the Evidence-based Practice Center (EPC) program.<sup>49</sup> Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias. Table 5 describes the grades of evidence that can be assigned. These grades reflect the strength of the body of evidence to answer KQs on the comparative effectiveness, efficacy, and harms of the interventions included in our review. Grades do not refer to the general efficacy or effectiveness of interventions. Two reviewers will assess each domain for each key outcome, and differences will be resolved by consensus.

We will grade the strength of evidence for the outcomes deemed to be of greatest importance to decisionmakers and those most commonly reported in the literature. We expect these to include medication adherence, clinical outcomes, and health utilization.

**Table 5. Definitions of the grades of overall strength of evidence<sup>49</sup>**

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

## G. Assessing Applicability

We will use guidance from Atkins and colleagues<sup>50</sup> to assess the applicability of findings. Specifically, we will review and evaluate the following characteristics that may limit applicability:

- **Population**

1. Narrow eligibility criteria or exclusion of patients with comorbidities
2. Large differences between demographics of the study population and community patients
3. Narrow or unrepresentative disease severity, stage of illness, or comorbidities

- **Interventions**

1. Intensity and delivery of behavioral interventions that may not be feasible for routine use
2. Highly selected intervention team or level of training/proficiency not widely available

- **Outcomes**

1. Composite outcomes that mix outcomes of different significance
2. Short-term or surrogate outcomes

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## VI. Definition of Terms

Not applicable.

## VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

## VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit

about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

## **IX. Key Informants**

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## **X. Technical Experts**

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes, as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind or contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review or peer review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## **XI. Peer Reviewers**

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for comparative effectiveness reviews (CERs) and Technical Briefs, be published three months after the publication of the Evidence report.

Potential reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

