Evidence-based Practice Center Systematic Review Protocol

Project Title: Screening, Behavioral Counseling, and Referral in Primary Care to Reduce Alcohol Misuse

Amendment Date(s) if applicable: Not applicable
(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

Alcohol misuse, which includes the full spectrum from drinking above recommended limits (i.e., risky/hazardous drinking) to alcohol dependence,[1-3] is associated with numerous health and social problems and more than 85,000 deaths per year in the United States.[4-5] *Risky or hazardous drinkers* consume alcohol above daily, weekly, or per-occasion amounts.[5] *Harmful use* is defined by the ICD-10[6-7] as a pattern of drinking that is already causing damage to health. The damage may be either physical (e.g., liver damage from chronic drinking) or mental (e.g., depressive episodes secondary to drinking).

The *Diagnostic and Statistical Manual of Mental Disorders* (4th Edition, Text Revision; DSM-IV-TR)[8] defines *alcohol abuse* as a maladaptive pattern of use leading to clinically significant impairment or distress that meets at least one of the following criteria: use results in failure to fulfill occupational or social obligations due to drinking; use occurs in physically hazardous situations or leads to recurrent legal problems; or use continues despite persistent social or interpersonal problems.

Alcohol dependence is defined as a maladaptive pattern of use leading to clinically significant impairment or distress that meets at least three of the following criteria: tolerance; withdrawal; a great deal of time spent obtaining alcohol, using it, or recovering from its effects; important activities given up or reduced because of alcohol; drinking more or longer than intended; persistent desire or unsuccessful efforts to cut down or control alcohol use; or use continued despite knowledge of having a psychological problem caused or exacerbated by alcohol. According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA),

- men may be at risk for alcohol-related problems if their alcohol consumption exceeds 14 standard drinks per week or 4 drinks per day; and
- women may be at risk if they have more than 7 standard drinks per week or 3 drinks per occasion.[9]

A standard drink is defined as one 12-ounce bottle of beer, one 5-ounce glass of wine, or 1.5 ounces of distilled spirits.[10,11]

Hazardous drinking and alcohol-related disorders are a widespread public health problem in the United States. In 2007, the number of alcoholic liver disease-related deaths was 14,406 and the number of alcohol-induced deaths, excluding accidents and homicides, was 23,199.[12] In 2008, 11,773 people were killed in alcohol-impaired-driving crashes.[13] These fatalities accounted for 32 percent of all motor vehicle traffic fatalities in the United States. Risky or harmful drinking that goes unrecognized can further complicate the assessment and treatment of other medical and psychiatric conditions.[14]

Currently, an estimated 50 percent of adults 18 years of age and older are regular drinkers.[15] About 18 percent of adolescent boys and 14 percent of adolescent girls from 12 to 17 years of age reported drinking before age 13.[16] Although often underreported, alcohol use remains common among older people. An estimated 6 percent of older adults are considered to be heavy users of alcohol.[17] Lastly, in a recent survey, 11.8 percent of pregnant women in the United States reported recent use of alcohol.[18]

It is generally accepted that less severe alcohol problems (e.g., risky/hazardous drinking) are appropriate for brief interventions in primary care, whereas more severe problems, particularly alcohol abuse and dependence, may require specialty addiction treatment.[1,5,19] However, specialty treatment services may be in short supply, and some people may not be willing to follow up with specialty treatment services. Consequently, primary care physicians may sometimes provide the only care that people with alcohol abuse or dependence receive. Given that alcohol-related problems can cause significant morbidity and mortality, early identification and secondary prevention of alcohol problems by using screening and brief interventions in primary care have been increasingly advocated.[20-22] However, these recent recommendations do not appear to be based on systematic reviews of the evidence, and they lack standardization regarding the practice of brief intervention.

A range of risky drinkers (4–29%) has been found across multiple primary care populations, with prevalence estimates of 0.3 to 10.0 percent for harmful drinkers and 2.0 to 9.0 percent for alcohol dependence.[23] Rates of alcohol-use disorders among medical outpatients are similar to those seen in the general population and are generally higher in males and younger people of all races/ethnicities.[23-24] Physicians who provide ongoing care can assist patients who have current problems, or who are at risk for problems, through effective identification (screening and screening-related assessment), office-based interventions, and referrals to specialty services as needed.[25] Patients receiving referrals to specialty care based on positive screening results appear more likely to accept appointments for alcohol-related counseling than those receiving usual care.[26]

Evidence exists for the effectiveness of screening for early identification of alcohol-related disorders and interventions for alcohol problems in medical settings.[27] For example, brief interventions in the primary care setting have shown a net reduction in alcohol consumption of 12 to 34 percent.[28] Patients are often more receptive and ready to change than clinicians might expect.[20] However, screening and treatment rates remain low. One study of primary care physicians found that although most (88%) reported asking their patients about alcohol use, only 13 percent used standardized screening instruments.[29] Another study found that patients with alcohol dependence received the recommended quality of care, including assessment and referral to treatment, only about 10 percent of the time.[30] Less than a quarter of people with alcohol-related disorders ever seek help for these conditions; higher proportions of women than men seek help, despite the higher prevalence of alcohol-related disorders in men.[14] Most patients who misuse alcohol receive care from their general practitioner or primary care provider, where they represent about one-fifth of patients seen, a proportion similar to the proportions seen for diabetes and hypertension.[14]

In a recent clinician's guide to the NIAAA guidelines,[20] the authors explain that many primary care physicians are familiar with counseling at-risk drinkers but choose to refer most patients to specialized rehabilitation programs. These programs may not be appropriate for problem drinkers who have risky or harmful alcohol use but do not meet the DSM-IV-TR criteria

for abuse or dependence. Even if patients accept a referral and complete a rehabilitation program, about one-third will not respond to treatment.[31]

The American Society of Addiction Medicine recommends that the services of primary care physicians and other primary health care providers include, at a minimum, the provision of these four elements of care[32]:

1. Assessment of the nature and extent of alcohol, nicotine, and other drug use by patients, with consistency of data collection and documentation akin to the consistency of assessment and documentation of vital signs.
2. Routine screening for the presence of alcohol, nicotine, or other drug use problems in patients, as well as screening for risk factors for development of alcohol, nicotine, and other drug dependence.
3. Appropriate intervention by the primary care provider.
4. Ongoing general medical care services to persons who manifest alcohol, nicotine, or other drug problems, including dependence.

Commonly used screening tools to identify alcohol misuse include but are not limited to the following:

- Alcohol Use Disorders Identification Test (AUDIT) and its abbreviated versions, including the AUDIT-C.
- Cut-down, Annoyed, Guilty, Eye-opener (CAGE) questionnaire.
- Michigan Alcoholism Screening Test (MAST) and its abbreviated and population-specific versions.
- Rapid Alcohol Problems Screen (RAPS).
- Tolerance, Annoyed, Cut-down, Eye-opener (T-ACE) and Tolerance, Worried, Eye-opener, Amnesia, Kut-down (TWEAK) questionnaires, which are based on the CAGE questionnaire and designed for screening pregnant women.
- Versions of the single-question screening recommended by NIAAA, also called the Single Alcohol Screening Question (SASQ).
- Alcohol-Related Problems Survey (ARPS), shortened version (shARPS)
- The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), which was developed by the World Health Organization.

Behavioral interventions and patient education are often used for patients who have less severe alcohol use (i.e., risky/hazardous/harmful drinking).[5] Brief interventions generally aim to moderate a patient's alcohol consumption to sensible levels and to eliminate harmful drinking practices, rather than to insist on complete abstinence. There is ongoing debate about what exactly constitutes a brief intervention.[33] The Substance Abuse and Mental Health Services Administration (SAMHSA) defines *brief intervention* as "a single session or multiple sessions of motivational discussion focused on increasing insight and awareness regarding substance use and motivation toward behavioral change."[34] The assumption underlying brief interventions is that reducing overall alcohol consumption or improving drinking patterns toward safer use will lower the risk of medical, social, and psychological problems.[35] These interventions range from very brief interventions within a primary care visit to multicontact interventions that entail multiple,

often more lengthy, visits and nonvisit contacts over an extended period.[1] Brief alcohol interventions can include the following:

- Motivational interviews of varying length and number
- Cognitive behavioral therapy
- Self-completed action plans
- Written health education or self-help materials
- Requests to keep drinking diaries
- Written personalized feedback
- Followup telephone counseling
- Exercises to complete at home

In 2004, the U.S. Preventive Services Task Force (USPSTF) developed guidelines for screening and behavioral counseling interventions in primary care to reduce risky/harmful alcohol use.[19] The USPSTF makes a distinction between screening and screening-related assessment:

- Screening: identifying patients with probable risky/harmful alcohol use.
- Screening-related assessment: confirming screening results and distinguishing patients suitable for brief interventions from those needing specialty care referral

In 2004, the USPSTF also recommended the following[19]:

- Screening and behavioral counseling interventions to reduce alcohol misuse by adults, including pregnant women, in primary care settings. Grade: B Recommendation
- Evidence is insufficient to recommend for or against screening and behavioral counseling interventions to prevent or reduce alcohol misuse by adolescents in primary care settings. Grade: I Statement

The original systematic review conducted by the Oregon Evidence-based Practice Center covered the literature through February 2003 and addressed nonpregnant adults, pregnant women, and adolescents in primary care settings. The results of this systematic review, which were published in 2004, were used as the basis for the 2004 USPSTF recommendations discussed above. Several agencies have subsequently published clinical practice guidelines, including the Institute for Clinical Systems Improvement (2009),[22] the Michigan Quality Improvement Consortium (2009),[21] SAMHSA (2009),[36] and NIAAA (2005).[9,33] None of the recent guidelines appear to be based on a systematic review of the evidence. Lastly, guidelines approach the subject of brief alcohol interventions differently; there does not appear to be one standardized approach for the practice of brief intervention.

The main objective for this report is to conduct a systematic review of the effectiveness of screening followed by behavioral counseling, with or without referral, for alcohol misuse in primary care settings. We will update the evidence review produced for the USPSTF in 2004 with some revisions and expansions to the scope of the review. This new comparative effectiveness review (CER) adopted nearly all of the Key Questions (KQs) identified in the

earlier systematic review, titled Behavioral Counseling Interventions in Primary Care to Reduce Risky/Harmful Alcohol Use.[2] In addition, a number of important changes are included:

- We decided to include the full spectrum of alcohol misuse, expanding the CER to include alcohol abuse and dependence.
- We expanded the eligible settings from traditional primary care to also include settings with primary care-like relationships (e.g., infectious disease clinics for people with HIV).
- We added additional outcomes of interest to our populations, interventions, comparators, outcomes, timing, and settings (PICOTS) and analytic framework.
- We added "referral" as an intervention of interest and changed the title to reflect this addition.

II. The Key Questions

Question 1

What is the direct evidence that screening for alcohol misuse followed by a behavioral counseling intervention, with or without referral, leads to reduced morbidity (e.g., alcohol-related morbidity, alcohol-related accidents and injuries), reduced mortality, or changes in other long-term (6 months or longer) outcomes (e.g., health care utilization, sick days, costs, legal issues, employment stability)?

Question 2

How do specific screening modalities compare with one another for detecting alcohol misuse?

Question 3

What adverse effects are associated with screening for alcohol misuse and screening-related assessment?

Question 4

a. How do behavioral counseling interventions, with or without referral, compare with usual care for improving intermediate outcomes (e.g., change in mean number of drinks per drinking day, number of heavy drinking episodes) for people with alcohol misuse as identified by screening?

b. How do specific behavioral counseling approaches, with or without referral, compare with one another for improving intermediate outcomes for people with alcohol misuse as identified by screening?

Question 5

What adverse effects are associated with behavioral counseling interventions, with or without referral, for people with alcohol misuse as identified by screening?

Question 6

How do behavioral counseling interventions, with or without referral, compare with one another and with usual care for reducing morbidity (e.g., alcohol-related morbidity, alcohol-related accidents and injuries), reducing mortality, or changing other long-term (6 months or longer) outcomes (e.g., health care utilization, sick days, costs, legal issues, employment stability) for people with alcohol misuse as identified by screening?

Question 7

To what extent do health care–system influences promote or hinder effective screening and interventions for alcohol misuse?

PICOTS criteria for the KQs above:

- **Population(s):**

  Adolescents and adults who are 12 years of age or older, including subgroups of pregnant women, adolescents, college students, adults >65 years, racial/ethnic minorities (e.g., Latinos, Native Americans, African Americans), people with co-occurring mental health disorders or chronic medical conditions, people with different severity/levels of alcohol misuse (e.g., risky drinking vs. dependence) and veterans with alcohol misuse.

  Alcohol misuse includes risky or hazardous drinking, harmful drinking, alcohol abuse, and alcohol dependence.

- **Interventions:**

  Office-based screening for alcohol misuse followed by behavioral counseling interventions intended primarily to reduce alcohol intake (e.g., motivational interviews, cognitive behavioral therapy, action plans, written materials, and personalized feedback, among others) with or without referral.

  Studies using office-based screening for alcohol misuse with one of the following instruments will be eligible for inclusion:

  - Alcohol Use Disorders Identification Test (AUDIT) and its abbreviated versions
  - Cut-down, Annoyed, Guilty, Eye-opener (CAGE) questionnaire
  - Michigan Alcoholism Screening Test (MAST) and its abbreviated and population-specific versions
  - Rapid Alcohol Problems Screen (RAPS)
  - Tolerance, Annoyed, Cut-down, Eye-opener (T-ACE) and Tolerance, Worried, Eye-opener, Amnesia, Kut-down (TWEAK) questionnaires, which are based on the CAGE questionnaire and designed for screening pregnant women
  - Single-question screening recommended by NIAAA, also called the Single Alcohol Screening Question (SASQ)

- Alcohol-Related Problems Survey (ARPS), shortened version (shARPS)
- Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)

In addition, studies using one or more questions related to quantity and/or frequency of alcohol use will be eligible.

- **Comparators:**
  - Different combinations, approaches, and modalities for the above interventions (KQs 1, 4b, 5, 6, and 7)
  - Usual care (as defined by the study, representing however a particular practice or setting is providing care for patients/subjects who do not receive an intervention) (KQs 1, 4a, 5, 6, and 7)
  - Office-based screening for alcohol misuse with another of the screening instruments above (KQs 2 and 3)

- **Outcome measures:**
  - Intermediate outcomes

    1. Rates of alcohol use, reported as the mean number of drinks per week
    2. Percentage of participants without binge drinking
    3. Percentage of participants who achieve the recommended drinking levels or patterns
    4. Receipt of and followup with referrals
    5. Abstinence from any use of alcohol

  - Health outcomes, utilization outcomes, and other end points

    6. Alcohol-related morbidity and mortality
    7. All-cause mortality
    8. Alcohol-related accidents and injuries
    9. Health care utilization
    10. Sick days
    11. Costs
    12. Legal issues
    13. Employment stability
    14. Quality of life

  - Potential adverse effects of interventions

    15. Anxiety
    16. Stigma, labeling, and/or discrimination
    17. Interference with the doctor-patient relationship
    18. Opportunity costs/time
    19. Increased smoking, and/or illegal substance use

- **Timing:**

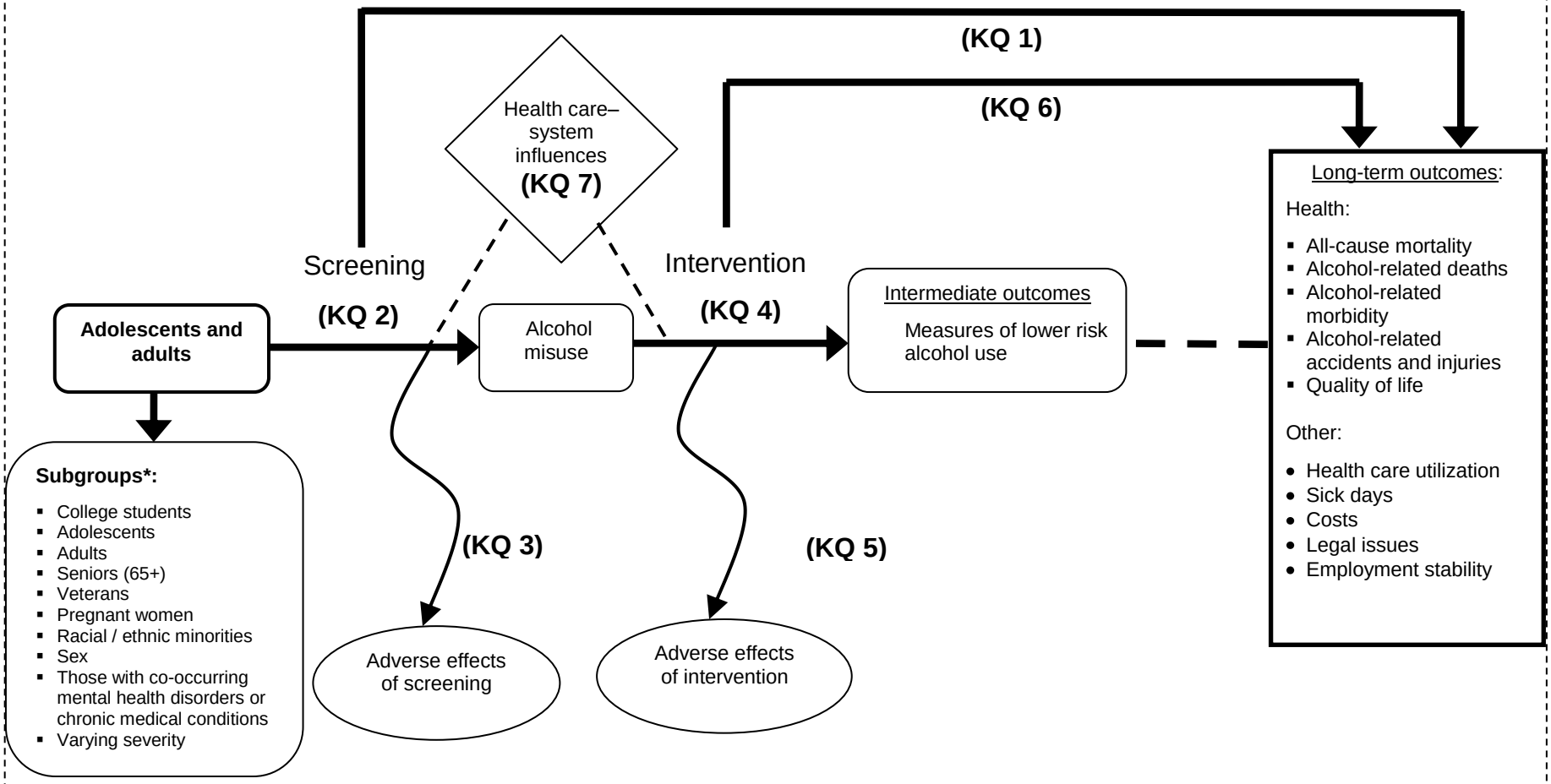
  Outcome assessment at least 6 months after randomization (or from receipt of the intervention for nonrandomized controlled trials)

- **Settings:**

  - Traditional primary care settings (internal medicine, family medicine, pediatrics, obstetrics/gynecology, or college and university health clinics).
  - Settings with a primary care-type relationship that may be applicable to traditional primary care settings (e.g., infectious disease clinics for people with HIV, oncology clinics for people with cancer).
  - Studies enrolling more than 20 percent of subjects recruited via methods other than office-based screening will be excluded.

III. Analytic Framework

Figure 1. Analytic framework for screening, behavioral counseling, and referral in primary care to reduce alcohol misuse



Source: www.effectivehealthcare.ahrq.gov
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*We will search for evidence on subgroups, and we will describe evidence on these subgroups within the Key Questions (KQs). This may include stratifying results by various subgroups if sufficient evidence is found.

Source: www.effectivehealthcare.ahrq.gov
Published Online: July 21, 2011

IV. Methods

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

Table 1 presents the inclusion/exclusion criteria for this review. We do not repeat all of the PICOTS information related to the inclusion/exclusion criteria.

Table 1. Inclusion/exclusion criteria

Category	Criteria	
	Inclusion	**Exclusion**
Population	Adults and/or adolescents (ages 12 years and older) with alcohol misuse*	Children (under 12 years of age)
Geography	No limits	
Time period	1985–present; searches to be updated after draft report goes out for peer review	
Length of followup	At least 6 months (24 weeks)	Fewer than 6 months
Settings	Traditional primary care settings and settings with a primary care-type relationship that may be applicable to traditional primary care settings as described in the PICOTS	All other settings Studies enrolling more than 20% of subjects recruited via methods other than office-based screening
Interventions	As defined above in the PICOTS Studies must both screen and intervene for alcohol misuse	Screening without subsequent intervention (e.g., case-finding studies with no followup) Interventions delivered without prior screening Interventions using devices (e.g., electroconvulsive therapy) Pharmacotherapy studies
Outcomes	Intermediate outcomes, health outcomes, utilization outcomes, long-term outcomes, and adverse effects as listed above under the PICOTS	
Publication language	English	All other languages†
Admissible evidence (study design and other criteria)	Original research; eligible study designs include: • Randomized controlled trials, • Nonrandomized controlled trials with concurrent eligible controls, and • Systematic reviews with or without meta-analyses. We will include systematic reviews and controlled trials for all outcomes. If we discover gaps in the systematic review and trial literature for KQ 6, we will search for prospective cohort studies with an eligible comparison group and sample size of at least 500. We will not include observational studies for other KQs due to the risk of bias being too high to provide valid and reliable evidence for the other KQs.‡ For KQ 1, we will include studies that assign subjects to screening vs. another screening approach, no screening, or usual care. For KQ 2,§ like the previous USPSTF review, we will	Case series Case reports Nonsystematic reviews Editorials Letters to the editor Articles rated poor during quality assessment Studies with historical, rather than concurrent, control groups

Category	Criteria	
	Inclusion	**Exclusion**
	assess the approaches used for screening by using included systematic reviews and within the included studies (of screening followed by an intervention). We will supplement the findings with information from other reviews, if necessary. For KQs 3, 5, and 7, we will evaluate the information within the included systematic reviews and trials. For KQs 4 and 6, we will include studies that assign subjects that had a positive screening test to an intervention of interest vs. at least one eligible comparator.	

*Alcohol misuse includes risky or hazardous drinking, harmful drinking, alcohol abuse, and alcohol dependence.
† Due to limited time and resources, we only included studies published in English.
‡Observational studies that compare screening for alcohol misuse with no screening or that compare various types of screening have a very high risk of selection bias and confounding. We feel that the results should not be used to make decisions.
§KQ2 will address which screening modalities (if any) are capable of distinguishing people with dependence from those with less severe alcohol misuse, how the screening instruments compare for various subpopulations (e.g., pregnant women, adults over 65), and general characteristics of the screening tests (e.g., number of questions, sensitivity, specificity).
Abbreviations: KQ = key question; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; USPSTF = U.S. Preventive Services Task Force.

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 on alcohol misuse by using a variety of terms, medical subject headings (MeSH), and major headings and limiting the search to English-language and human-only studies. Relevant terms are listed in *Table 2*. We will also search the Cochrane Library, the Cochrane Central Trials Registry, the Cumulative Index to Nursing and Allied Health Literature, and PsycInfo by using analogous search terms. We will conduct quality checks to ensure that the known studies (i.e., studies included in the previous review on alcohol misuse and those identified during Topic Nomination and Refinement) are identified by the search. If they are not, we will revise and rerun our searches.

We will *not* simply conduct one search starting from where the 2004 systematic review on alcohol misuse left off. Rather, since our review has some differences in scope (described above on page 5), we will search the literature published in 1985 and later. This 1985 search date was selected based on the earliest publication date found in previous systematic reviews (which was 1988) and expert opinion about when the earliest literature on this topic was published.

We will search the "gray literature" for unpublished studies relevant to this review and will include studies that meet all the inclusion criteria and contain enough methodological information for assessment of internal validity/quality. Potential sources of gray literature

include ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform, and pharmaceutical companies' dossiers (for pharmacotherapies of interest).

We will review our search strategy with the Technical Expert Panel (TEP) and supplement it as needed according to their recommendations. In addition, to attempt to avoid retrieval bias, we will manually search the reference lists of landmark studies and background articles on this topic to look for any relevant citations that might have been missed by electronic 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 described above.

Table 2. PubMed literature search terms

Population	"Alcohol-Related Disorders" [MeSH] OR "Alcohol Drinking" [MeSH] OR "Alcoholism" [MeSH] OR "drinking behavior" [MeSH Terms] OR problem drink* OR heavy drink* OR alcohol problem* OR risky drink* OR at-risk drink* OR alcohol depend* OR excessive drink* OR excessive alcohol* OR "alcohol consumption" [All Fields] OR alcohol addition* alcohol misuse OR alcohol abuse OR hazardous alcohol* OR hazardous drink* OR harmful alcohol* OR harmful drink* OR (("drinking"[tiab] OR "drinkers"[tiab]) AND "alcohol"[tiab])
Interventions*	"alcohol reduction" OR brief intervention* OR early intervention* OR minimal intervention* OR alcohol therap* OR alcohol treatment* OR harm reduc* OR ("screening"[All Fields] AND alcohol) OR ("counseling"[All Fields] AND alcohol) OR controlled drink* OR "intervention"[All Fields] OR secondary prevention* OR "general practitioner's advice" OR (("health education"[MeSH Terms] OR "health education"[All Fields]) AND ("pamphlets"[MeSH Terms] OR "pamphlets"[All Fields])) OR ("counseling"[All Fields] AND drink*) OR ("screening"[All Fields] AND drink*)OR "Mass Screening"[MeSH] OR "Counseling"[Mesh] OR "Psychotherapy"[Mesh] OR SBIRT[tiab] OR "counseling"[tiab]
Limits	Humans Clinical Trial; Meta-Analysis; Randomized Controlled Trial; Review; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Comparative Study; Controlled Clinical Trial; Multicenter Study English language Publication Date from 1985/01/01 to [date of search]

*On April 28, 2011, we amended the protocol to exclude studies of pharmacotherapy for alcohol dependence. However, because [our] scope included pharmacotherapy at the time of the searches, the following terms were also included: "naltrexone," "Revia," "Vivitrol," "acamprosate," "Campral," disulfiram," "Antabuse," and "Alcohol Deterrents" [MeSH].

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 without 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® bibliographic database (Thomson Reuters, New York, NY).

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. We will design data abstraction forms to gather pertinent information from each article, including characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. 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 the USPSTF (ratings: good, fair, poor) and the University of York Centre for Reviews and Dissemination.[37,38] In general terms, a "good" study has the least bias, and its results are considered to be valid. A "fair" study is susceptible to some bias but probably not sufficient enough to invalidate its results. A "poor" study has significant bias (e.g., stemming from serious errors in design or analysis) that may invalidate its results. If observational studies are included for KQ 6, we will perform quality assessments by using the criteria outlined by Deeks and colleagues.[39]

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. We will give a good quality rating to studies that meet all criteria. Fair quality ratings will be given to studies that presumably fulfill all quality criteria but do not report their methods sufficiently to answer all of our questions. We will give a poor quality rating to studies that have a fatal flaw (defined as a methodological shortcoming that leads to a very high risk of bias) in one or more categories and will exclude them from our analyses.

E. Data Synthesis

Prioritization and/or categorization of outcomes will be determined by the research team with input from TEP members. 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.

In order to determine whether quantitative analyses are appropriate, we will assess the clinical and methodological heterogeneity of the studies under consideration following established guidance.[40] We will do this by qualitatively assessing the PICOTS of the included studies, looking for similarities and differences. We will not plan to combine studies that enrolled only pregnant women or adolescents with those that enrolled all adults. When quantitative analyses are not appropriate (e.g., due to 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 this review will be synthesized qualitatively.

We plan to stratify analyses and/or perform subgroup analyses when possible and appropriate. Planned stratifications or categories for subgroup analyses include geographic location of studies (United States vs. all other countries), severity of alcohol misuse (dependence, abuse, etc.), and age (adolescents vs. adults).

F. Grading the Evidence for Each Key Question

We will grade the strength of evidence based on the guidance established for the Evidence-based Practice Center Program.[41] 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 3 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer KQs on the comparative effectiveness, efficacy, and harms of the interventions included in this 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 intermediate outcome measures of alcohol use, health outcomes, and mortality.

Table 3. Definitions of the grades of overall strength of evidence[41]

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 assess applicability of the evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[42] We will use the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence include the following: age of enrolled populations; sex of enrolled populations (e.g., few women may be enrolled in the studies); race/ethnicity of enrolled populations; few studies evaluating pregnant women, the elderly, or adolescents; and the use of interventions that may be difficult to incorporate into routine practice for many providers (i.e., they require substantial resources or time, they may be delivered by research staff rather than existing staff in the practice).

H. Contextual Question

For this report, we will address the question of whether there are effective treatments for alcohol dependence as a "contextual question" (including whether pharmacotherapy is effective for alcohol dependence). Further description of contextual questions from the *U.S. Preventive Services Task Force Procedure Manual* (hereafter *USPSTF Procedure Manual*) is provided in the two paragraphs below.[43] Although we will not systematically address the efficacy/effectiveness of various treatments (e.g., pharmacotherapy, 12-step programs, specialized outpatient treatment programs) for alcohol dependence with a KQ, we plan to summarize the available evidence regarding such treatments in the Introduction and/or Discussion sections. To do so, we will rely on previously published reviews and expert input. We will also address the issue of whether there is known evidence of efficacy of pharmacotherapy for patients with dependence identified by screening in the primary care setting (as opposed to treatment seekers or those identified by other methods) or for subjects treated in primary care settings.

The following two paragraphs are from Section 3.2 of the *USPSTF Procedure Manual*[43]

> Contextual questions are not key questions associated with the analytic framework; however, they represent issues in an updated review for which the USPSTF needs a valid but not necessarily systematic summary of current research in order to provide the context for its vote and recommendation statement. Contextual questions may elicit a range of different types of information, including: (1) updated information for a key question that is not being systematically updated; (2) contextual information on natural history, current practice, prevalence and risk groups, or other aspects of the service for which it is strongly believed there will not be information, but which are part of the Task Force's considerations (e.g., screening interval, ages when screening should be stopped; or newer technologies for screening and/or intervention); or (3) cost-effectiveness.
>
> Contextual questions are not necessarily addressed systematically; however, the approach taken may meet criteria for a systematic review. Comprehensive literature searches are not generally undertaken specifically to answer these questions. Information for contextual questions can be gathered in a variety of ways: (1) through targeted literature searches, (2)

from authoritative surveys or reviews, (3) from expert input, and (4) opportunistically, while reviewing comprehensive literature searches for key questions. Contextual questions are not listed as separate questions in the methods section of the report and are not reported in the results section. The information resulting from non-systematic review should be included as part of the introduction or in the discussion section, and related as appropriate to the results of the systematic review.

V. References

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VI. Definition of Terms

Alcohol misuse includes risky or hazardous drinking, harmful drinking, alcohol abuse, and alcohol dependence.

Risky or *hazardous drinkers* are at risk from consumption that exceeds daily, weekly, or per occasion thresholds.[5,23,44]

Harmful use is defined by the ICD-10[6-7] as a pattern of drinking that is already causing damage to health. The damage may be either physical (e.g., liver damage from chronic drinking) or mental (e.g., depressive episodes secondary to drinking).

Alcohol abuse is a maladaptive pattern of use leading to clinically significant impairment or distress that meets at least one of the following criteria: use results in failure to fulfill occupational or social obligations due to drinking; use occurs in physically hazardous situations or leads to recurrent legal problems; use continues despite persistent social or interpersonal problems.[11]

Alcohol dependence is a maladaptive pattern of use leading to clinically significant impairment or distress that meets at least three of the following criteria: tolerance; withdrawal; a great deal of time spent obtaining alcohol, using it, or recovering from its effects; important activities given up or reduced because of alcohol; drinking more or longer than intended; persistent desire or unsuccessful efforts to cut down or control alcohol use; use continued despite knowledge of having a psychological problem caused or exacerbated by alcohol.[11]

A standard drink is defined as one 12-ounce bottle of beer, one 5-ounce glass of wine, or 1.5 ounces of distilled spirits.[10-11]

VII. Summary of Protocol Amendments

Not applicable.

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 (from December 14, 2010 through January 11, 2011 and finalized by the EPC after review of the comments. Based on public comments and input from TEP members, we changed the term "unhealthy alcohol use" (which we used in the initial draft of our KQs) back to "alcohol misuse" (which was used in the original report in 2004).

Based on public and TEP input, we excluded pharmacotherapy. Pharmacotherapy for alcohol dependence in the primary care setting was considered for possible addition to this update. Because our scope included pharmacotherapy at the time of the initial searches, the following terms were also included: "naltrexone," "Revia," "Vivitrol," "acamprosate," "Campral," disulfiram," "Antabuse" and "Alcohol Deterrents"[MeSH].

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 healthcare 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 TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multi-disciplinary 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 nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public 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 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.