Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Screening for Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Amendment Date(s) if applicable: October 24, 2011

(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

Methicillin-resistant *Staphylococcus aureus* (MRSA) first emerged as a clinically relevant human pathogen more than 3 decades ago.[1] The aggressive bacterium was first detected in hospitals and other health care facilities where vulnerable hosts, frequent exposure to the selective pressure of intensive antimicrobial therapy, and the necessity for invasive procedures (which further compromise host defenses) created a favorable environment for dissemination. MRSA emerged as an important cause of health care–associated infections, particularly central line-associated bloodstream infection, ventilator-associated pneumonia, and surgical site infection. Despite the adoption of a number of measures to prevent spread, the incidence of MRSA infection at most U.S. hospitals has steadily increased over the past 20 years.[2] Complicating matters, the management of infection caused by MRSA remains a challenge for clinicians. A number of analyses suggest that MRSA infections are associated with increased mortality and cost of care when compared with those due to strains that are susceptible to methicillin. A meta-analysis by Cosgrove and colleagues identified a 2-fold increased risk of death associated with methicillin resistance.[3] Engemann and colleagues documented a significantly higher risk of poor outcomes and increased expense in managing patients with surgical site infection due to MRSA when compared with patients infected with antibiotic-susceptible strains.[4] Even the availability of newer pharmaceutical agents with specific activity against MRSA, including linezolid and daptomycin, has not lessened the burden of MRSA for patients and clinicians. The widespread use of these agents has been limited in part due tobecause of toxicity, expense, and uncertainty as to optimal indications.[5]

The management and control of MRSA has been further complicated by dramatic changes in the epidemiology of transmission and infection observed over the past 2 decades. Specifically, *S. aureus* strains resistant to methicillin, once exclusively linked to hospital care, have increasingly been detected among patients in the community who lack conventional risk factors for MRSA infection (such as prior antimicrobial therapy or invasive procedures).[6,7] These so-called community-associated MRSA (CA-MRSA) strains have demonstrated a predilection to affect specific populations. Clusters among schoolchildren and competitive athletes have been extensively described in both the scientific literature and the mass media.[5,8] CA-MRSA infection often manifests in characteristic clinical patterns—including aggressive skin and soft tissue infections (typically arising from an initial lesion often mistaken by patients and clinicians for a spider bite) and necrotizing pneumonia.[9] Extensive investigation has demonstrated a number of unique genetic and pathogenic features of CA-MRSA isolates that may provide insight into the epidemiology of these bacteria. CA-MRSA strains typically share a distinctive methicillin-resistance cassette that helps to explain the characteristic susceptibility of these strains to non–beta-lactam antimicrobial agents such as clindamycin and trimethoprim/sulfamethoxazole.[10] In addition, CA-MRSA isolates commonly overexpress a particular set of virulence factors, including the Panton-Valentine leukocidin.[11] While the specific relationship between these features and the unique clinical and epidemiological characteristics of CA-MRSA remain to be elucidated, the importance of these strains continues to grow. CA-MRSA has increasingly been linked to outbreaks of infection in hospitals and health care facilities, and there is some evidence that these strains are now the dominant cause of staphylococcal disease in some settings.[12]

Conventional strategies for the control of MRSA (whether hospital- or community-associated) have focused on the prevention of spread from patient to patient (horizontal transmission). It is generally acknowledged that environmental contamination and airborne transmission could plausibly play a minor role in transmission.[13,14] However, the overwhelming majority of staphylococcal spread (and of MRSA) likely comes about through a chain of transmission linking a colonized or infected patient and a previously unaffected patient by way of the hands or personal items of health care workers. With this in mind, the most common tools used to prevent the spread of MRSA involve the disruption of these points of contact.

The effectiveness of hand hygiene in preventing the spread of MRSA has been most convincingly demonstrated in quasiexperimental observational studies in which hand hygiene-promotion campaigns were associated with subsequent reductions in the incidence of MRSA among hospitalized patients. Pittet and colleagues demonstrated a significant reduction in MRSA bloodstream infections in one especially robust investigation.[15] The benefit of hand hygiene appears to be consistent, whether the use of soap and water or alcohol-based hand rubs is promoted.[16] The ease of adherence associated with the latter method suggests that this approach may be especially fruitful.

While hand hygiene remains the cornerstone of MRSA transmission-control efforts, the continued spread of the pathogen after initial introduction in most facilities has prompted efforts to identify more robust and effective strategies. The use of personal protective equipment—including the donning of gowns and gloves when interacting with patients colonized or infected with MRSA and the assignment of such patients to single rooms or to a room with a group of affected patients—has been widely promoted and adopted. Such isolation precautions now stand as the centerpiece in most authoritative guidelines regarding MRSA control.[17] Despite the broad consensus associated with the use of personal protective equipment for MRSA prevention, the specific evidence in support of this practice remains somewhat limited and indirect. Jernigan and colleagues noted a significant decrease in the risk of MRSA transmission when isolation precautions were implemented in a pediatric unit.[18] However, the fact that the study was conducted in the midst of a MRSA outbreak in the unit raises questions about the suitability of generalizing these findings to other circumstances, including settings in which MRSA is endemic. Moreover, a number of studies have examined the role of specific elements of isolation precautions (specifically, the use of gowns vs. gloves) with mixed results.[19]

Given the continued dissemination of MRSA at most U.S. hospitals, it is clear that these measures, as presently deployed, have been insufficient to check the spread of MRSA and other antibiotic-resistant pathogens. Much of the blame for this underperformance can likely be attributed to the poor adoption of these measures at most health care facilities. When rigorously assessed, adherence to hand hygiene standards is especially disappointing; many hospitals report a compliance rate of <50 percent among health care workers. The situation with PPE use and adherence to isolation precautions is difficult to know, as compliance has been less commonly studied and reported. However, a recent report found that despite the use of an electronic flag denoting the need for isolation precautions in the records of inpatients at an urban academic medical center, only 58 percent of such patients were placed in a private room and had appropriate signage posted on the door to the room.[20] Other analyses of actual compliance with the donning of gowns and gloves have been similarly disappointing.

A further important limitation of these approaches—and specifically the use of isolation precautions—relates to the potential negative consequences of these measures. A series of studies have associated isolation precautions with worsened outcomes in terms of safety and patient satisfaction.[21] In addition, questions have been raised about specific performance measures, such as the frequency with which patients on isolation precautions are visited by treating physicians and the timely recording of vital signs. While the methodology employed in some of these studies has been questioned, no rigorous definitive analysis has been completed to exonerate isolation precautions.[22]

Based on the failure of conventional control strategies to adequately control MRSA, more aggressive measures have been promoted in an effort to check the spread of this particularly virulent pathogen. In some European countries, an aggressive containment program, colorfully referred to as “search and destroy,” identifies contacts of colonized and infected patients in an effort to intercede to prevent dissemination.[23] While such draconian measures have not been widely adopted in most settings, some clinicians, scientists, and increasing numbers of public advocates and legislators have raised the call for more intensive efforts at MRSA control in the United States. Particular attention has been given to the potential value of active surveillance screening for MRSA. Because routine clinical cultures may identify as few as 18 percent of patients overtly infected with antibiotic-resistant organisms such as MRSA, there exists a large reservoir of patients who are silent carriers of these organisms. These individuals may serve as a reservoir for further transmission. With active surveillance, microbiological samples are obtained from at-risk patients even in the absence of signs or symptoms of infection in an effort to identify the underlying population of colonized individuals. In most cases, this involves the collection of a nasal swab, as the nares have been identified as a common sanctuary site for MRSA in colonized individuals. At some centers, additional sites may be sampled, depending on the population under examination (e.g., the umbilicus of newborns; the sites of invasive devices or wounds). By detecting the larger population of colonized individuals, at the very least conventional precautions can be implemented in a broader and more timely manner so as to interrupt horizontal transmission of MRSA. Detection of colonized patients also permits consideration of more aggressive interventions, including attempts at microbiological eradication or decolonization, as is discussed later.

The specific evidence in support of active surveillance for MRSA has been promising, although a number of questions remain regarding the suitability of this approach in some settings and populations. Some of the most compelling evidence for the effectiveness of active surveillance in controlling the spread of antibiotic-resistant organisms came from experience with vancomycin-resistant enterococcus. Rectal screening for this pathogen was associated with decreased transmission at the level of individual units and wards,[24] whole hospitals,[25] and even across an entire region.[26] For MRSA, a number of fairly rigorous studies have tested the hypothesis that identification of asymptomatic carriers can result in decreased MRSA transmission. Huang and colleagues reported their experience of adding active surveillance screening of patients in the intensive care unit to an already comprehensive control strategy (including hand hygiene promotion) and a bundle of interventions to prevent central line-associated bloodstream infection. Only the addition of active surveillance resulted in a statistically significant decline in the incidence of MRSA bloodstream infections.[27] In perhaps the most widely cited report of active surveillance for MRSA, Robicsek and colleagues describe ***Source: www.effectivehealthcare.ahrq.gov Published Online:*** *June 2, 2011* the impact of a staged implementation of screening, first among patients in an intensive care unit and ultimately involving all patients admitted to a three-hospital health care system in a Chicago suburb. With this approach, the prevalence and density of MRSA disease fell significantly among all patients.[28] However, this is not to say that the experience with active surveillance has been universally effective. Harbarth and colleagues found that active surveillance screening of surgical patients was not associated with a reduction in surgical site infections in a crossover-design study at a large Swiss center.[29]

A number of methodological issues have been raised about many of the studies of active MRSA surveillance, including both those that seem to support the practice and those that do not. These questions also reflect the methodological uncertainty about deploying the strategy in actual clinical practice. One key issue relates to the microbiological testing method applied. Early on, most surveillance programs relied on conventional culture methods. This approach, while reliable and familiar in the hands of most clinical laboratories, is plagued by the necessity of delayed availability of final results, in as much as culturing, subculturing, and formal susceptibility testing can require up to 5 to 6 days in some laboratories. Advances in culture methodology, including the use of chromogenic growth media, can shorten this waiting period, but still do not typically provide clinicians with information regarding the need for isolation precautions until a day or more after the samples are collected. Most recently, the advent of reliable and commercially available polymerase chain reaction techniques offer the promise of exceptionally rapid turnaround time for MRSA detection (often less than several hours). Farr has argued that without standardization and optimization to ensure rapid results from screening, comparisons regarding the relative effectiveness of active surveillance for MRSA are limited.[30] Some of the concerns about delayed screening results screening can be obviated by adopting a policy of early implementation of isolation precautions for all screened patients with the aim to discontinue these measures for those patients who test negative (irrespective of the assay employed). This so-called “guilty until proven innocent” approach, while sound from an epidemiological perspective, has presented logistical challenges at centers where the physical plant limits the availability of rooms and beds for such empirical isolation.

Determining the optimal approach once patients are identified as colonized with MRSA presents an even larger challenge to assessing the effectiveness of active MRSA surveillance. The impact of screening is likely to be exceptionally sensitive to the measures deployed once MRSA carriers are identified. As has been noted, adherence to basic prevention measures, such as hand hygiene and the use of personal protective equipment, is inconsistent in most settings in which compliance has been measured. Nonetheless, these very practices are central to the effectiveness of any active surveillance program. Simply stated, knowing which patients are colonized with MRSA should not be expected to affect the frequency of spread if adherence to transmission-control strategies remains inadequate. Surprisingly, even the most robust investigations of the effectiveness of active surveillance have not routinely described the frequency of compliance with hand hygiene and use of personal protective equipment. Similarly, other more intensive measures may dramatically affect the impact of a MRSA-screening program. For example, efforts to decolonize or eradicate MRSA from carrier patients through the use of systemic or topical antimicrobial agents should have an important effect on the likelihood of transmission. This practice has been applied in a number of settings for both MRSA and staphylococcal disease in general.[31] The results have been mixed, depending on the population under study, and the risk for emerging antibiotic resistance as the result of such efforts remains a concern. With this in mind, to try to determine the impact of a screening program without detailed information about the deployment of decolonization measures is an important limitation to the available studies and has engendered considerable confusion among clinicians and policymakers.

In light of the promising, but limited evidence in support of active MRSA surveillance and in consideration of the important methodological questions previously noted, a systematic review of the evidence appears to be both justified and timely. The importance of gaining a better understanding of the evidence is further highlighted by the increasing demand for better control of MRSA and a higher standard for prevention of hospital-acquired infections in general. Policymakers both within and outside of the U.S. health care system have heeded the degree of public concern surrounding these issues. The control of MRSA and other antibiotic-resistant bacteria has been highlighted as a likely target for pay-for-performance initiatives on the part of the U.S. Government and a number of private payers. The Joint Commission has highlighted the issue by identifying a National Patient Safety Goal regarding the control and prevention of antibiotic resistance. Perhaps most telling, some State jurisdictions in the United States have already mandated screening for MRSA. In some cases, these legislative mandates have been issued even in the face of direct opposition from clinical experts in the field.[32] It seems evident that the public and scientific debate regarding the merits and potential negative consequence of widespread MRSA screening will benefit from a systematic review of the available evidence.

II. The Key Questions

The draft Key Questions, developed during the Topic Refinement phase with input from Key Informants, were available for public comment on the Effective Health Care Program Web site. The comments highlighted the controversies surrounding MRSA screening and the challenges inherent in a review of this topic. Based on the comments received, no changes were made to the key clinical questions. This section, in response to the public comments, provides additional details regarding the scope of the report and notes a change in the analytic framework (Figures 1 and 2).

The review will examine MRSA-screening strategies that include screening with or without isolation and with or without attempted eradication/decolonization. The analytic framework had previously not illustrated the possibility that a patient who screens positive for MRSA would not be isolated but would instead be decolonized (Figure 1); in response to the comments received, the analytic framework has been modified to include this possibility (Figure 2). Decolonization in the absence of screening can also occur. However, because MRSA screening is the focus of this review, prevention, diagnostic, and/or treatment strategies that do not include screening will not be addressed. In addition, the optimal duration of isolation, the use of personal protective equipment by visitors, and the optimal decolonization regimen will not be formally evaluated. The systematic review, however, will distinguish among screening that uses a testing modality with a rapid turnaround time (results available on the same day the test is performed), screening that uses a testing modality with an intermediate turnaround time (results available next day to two days after the test is performed), and screening that uses a testing modality (typically, a culture) with a longer turnaround time (results available > 2 days after testing performed). The review will consider a variety of screening types (e.g., polymerase chain reaction, culture) and sites of screening (e.g., nares, umbilicus). However, it will not formally evaluate the comparative effectiveness of screening at different sites or the optimal number of sampling sites. Because the harms of not screening patients for MRSA are to expose them to the risk of MRSA acquisition, infection, morbidity, and mortality, this review will indirectly address the harms of not screening.

In the absence of universal surveillance, unscreened patients may serve as a reservoir of infection. When possible, this review will delineate those studies that achieved or attempted to achieve universal surveillance. In addition, transmission is related to the prevalence of MRSA colonization and the length of time exposed to colonized individuals. Thus, mathematical modeling may be required to determine where screening and decolonization might be effective, but this is beyond the scope of this comparative effectiveness review.

Finally, the commentators also noted the importance of the setting for MRSA screening, including inpatient, outpatient, and long-term care venues. This systematic review will focus on hospitalized patients (inpatients) and ambulatory patients (outpatients), and the analysis, when possible, will differentiate between hospitalized and ambulatory patients. While the report will not formally address patients in long-term care settings, it may capture the subset of this population that requires hospitalization or outpatient care.

In summary, this comparative effectiveness review will evaluate the benefits and harms of a MRSA-screening strategy in both inpatient and outpatient settings. Studies will be stratified by the turnaround time of the test used, rather than by the testing modality itself, as well as by whether or not the screening strategy also includes isolation and/or decolonization.

Question 1

Among ambulatory or hospitalized patients, what is the comparative effectiveness of a MRSA-screening strategy (screen, isolate, eradicate/decolonize)—when compared to no screening—on the incidence of MRSA infection?

Question 2

Among ambulatory or hospitalized patients, what is the comparative effectiveness of a MRSA-screening strategy (screen, isolate, eradicate/decolonize)—when compared to no screening—on morbidity, including complications of MRSA infection?

Question 3

Among ambulatory or hospitalized patients, what is the comparative effectiveness of a MRSA-screening strategy (screen, isolate, eradicate/decolonize)—when compared to no screening—on mortality?

Question 4

Among ambulatory or hospitalized patients, what is the comparative effectiveness of a MRS-screening strategy (screen, isolate, eradicate/decolonize)—when compared to no screening—on MRSA transmission as measured by new acquisition events?

Question 5

Among ambulatory or hospitalized patients, what are the harms of a MRSA-screening strategy (screen, isolate, eradicate/decolonize)—when compared to no screening—including allergic and nonallergic toxicity (e.g., hypotension), antimicrobial resistance, reduced quality of care, and medical errors?

Question 6

Among all ambulatory or hospitalized patients, what is the effect of a MRSA-screening strategy (screen, isolate, eradicate/decolonize)—when compared to no screening—on hospital resource utilization such as length of stay?

Eligibility Criteria

- **Population(s)**

  The patient population is all ambulatory and hospitalized patients. In addition, the following subpopulations will be evaluated:

  1. Patients admitted to a neonatal intensive care unit.
  2. Patients admitted to a pediatric intensive care unit.
  3. Patients admitted to an adult intensive care unit.
  4. Patients undergoing surgical procedures.

- **Interventions**

  1. A MRSA-screening strategy:

     a. That includes:

        (1). MRSA screening using a testing modality (typically, polymerase chain reaction) with rapid turnaround (results available on the same day as the testing is performed);

        or

        (2). MRSA screening using a testing modality with intermediate turnaround (results available 1 to 2 days after testing is performed);

        or

        (3). MRSA screening using a testing modality (typically, culture) with a longer turnaround time (results available >2 days after testing is performed);

     b. And that may include:

        (1). Isolation;

        and/or

        (2). Eradication/decolonization.

- **Comparator**

  No screening.

- **Outcomes**

- Intermediate outcomes: MRSA acquisition and infection.
- Health outcomes: morbidity (including complications of MRSA infection), case-fatality, mortality, quality of care for noninfectious conditions, and medical errors.
- Adverse events: adverse effects of screening and treatment, including allergic reactions, nonallergic toxicities, and resistance to antimicrobials.

- **Timing**

  Screening through intervention.

- **Settings**

  - Inpatient: hospital wards and intensive care units.
  - Outpatient: ambulatory clinics, urgent care centers, and emergency departments.

III. Analytic Framework

The figure below depicts the effects of MRSA screening on intermediate outcomes (including MRSA acquisition and infection) and health outcomes (including morbidity and mortality).

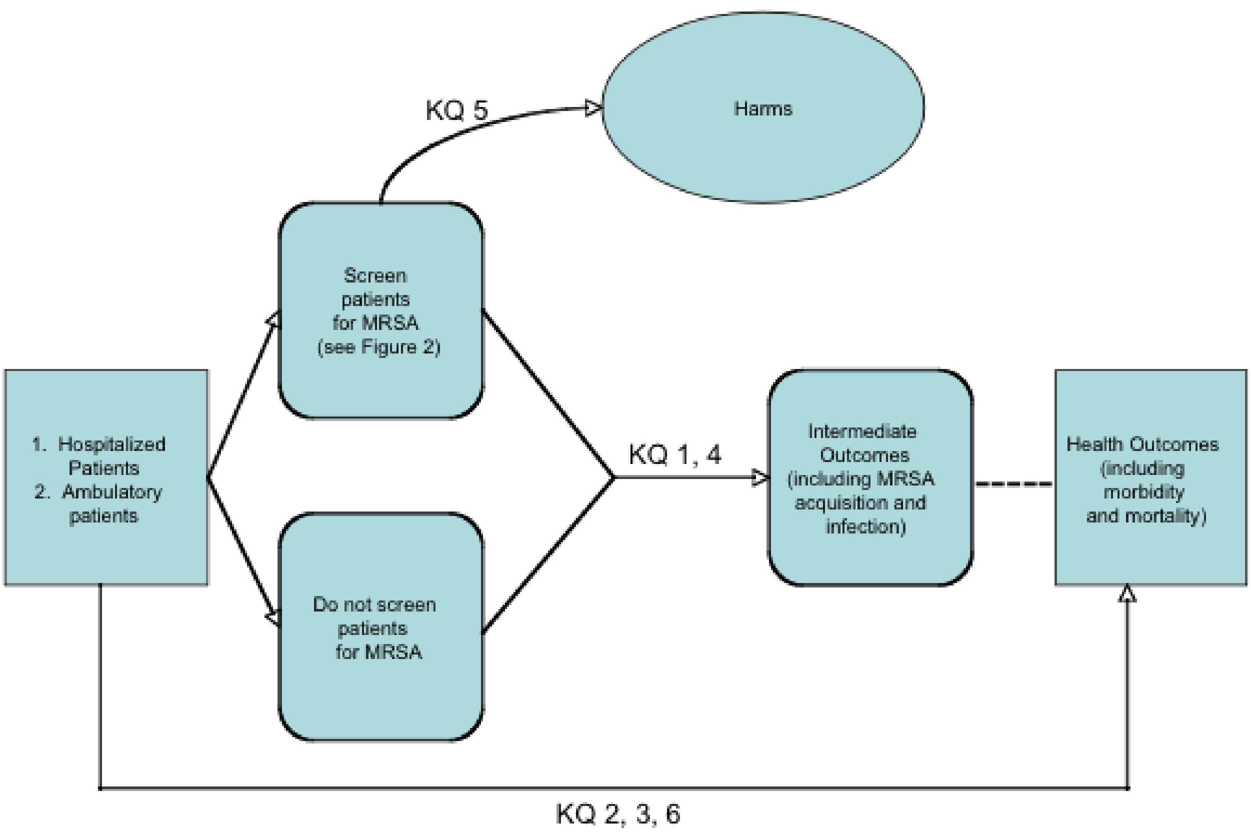

Figure 1. Analytic Framework for MRSA Screening

Abbreviations: KQ = key question; MRSA = methicillin-resistant *Staphylococcus aureus*.

The figure below depicts the effects of MRSA screening in detail. Once screened, patients may or may not be isolated while awaiting screening results. Once the screening test results are received, patients who screen positive may be isolated; patients who screen negative are not. Eradication/decolonization may be attempted in patients who screen positive. Intermediate outcomes of MRSA screening, including MRSA transmission and infection, are depicted in the figure. Health outcomes, including morbidity and mortality, are also depicted. The figure illustrates the potential harms of screening, including decreased room availability, decreased attention from health care personnel, antibiotic resistance, allergic reactions, and nonallergic toxicity.
Abbreviations: KQ = key question; MRSA = methicillin-resistant *Staphylococcus aureus*; Test + = positive MRSA-screening test result; Test – = negative MRSA-screening test result.

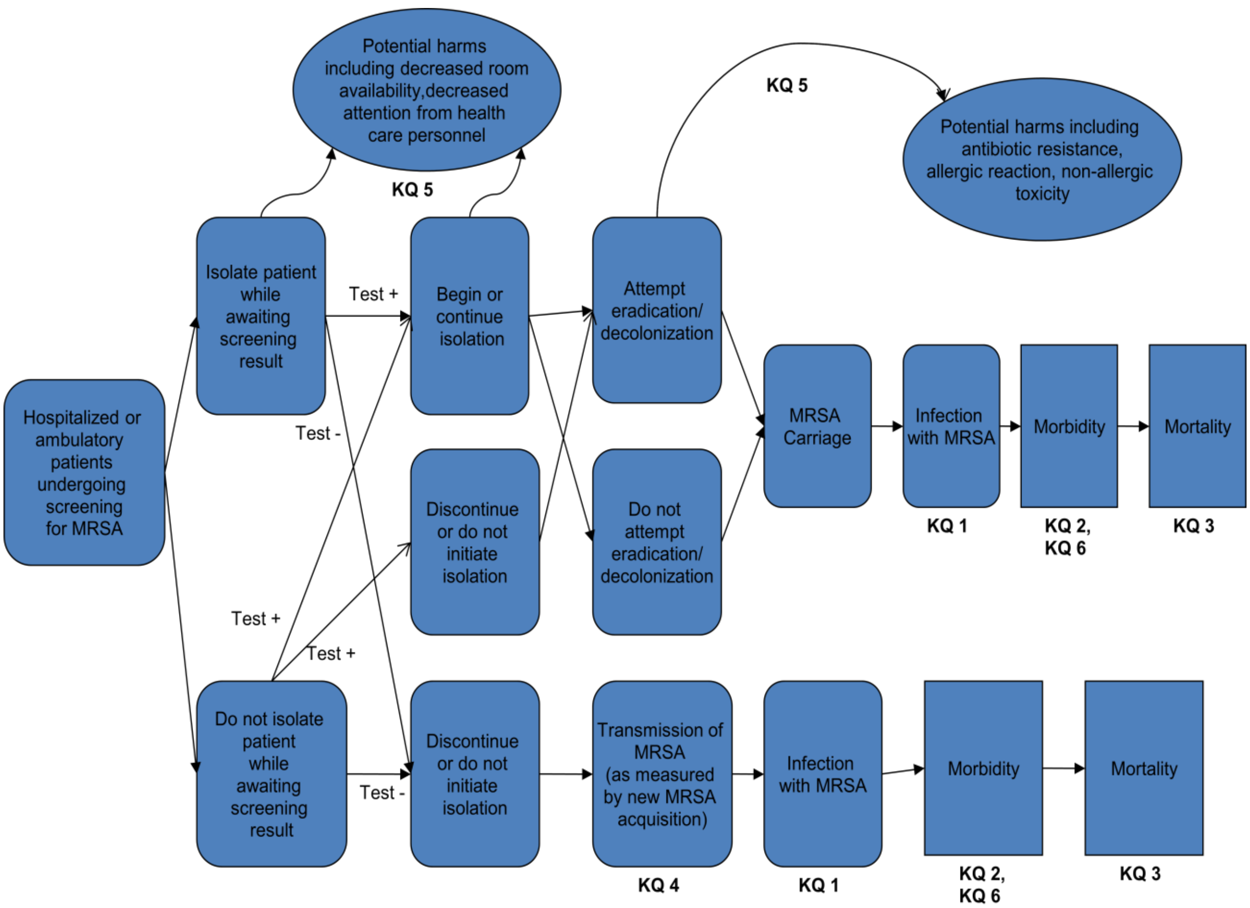

Figure 2. Analytic Framework for MRSA Screening

Source: www.effectivehealthcare.ahrq.gov
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IV. Methods

Practices to be followed in this review will be derived from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[33] (hereafter, *Methods Guide*) and its subsequent updates.

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

We will include randomized, controlled studies and nonrandomized, comparative studies (observational, case-control, and cohort studies) of populations, comparisons, interventions, and outcomes that were not adequately studied in controlled trials. We will also use observational studies to assess comparative effectiveness in populations not well represented in randomized controlled trials. To classify observational study designs, we will use the system developed by Briss and colleagues.[34]

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

The following databases will be searched for citations. The search will be limited to literature published from 1990 to the present because this is the evidence most applicable to current practice. The search will be limited to the English-language literature because in past projects, our Evidence-based Practice Center has found that the inclusion of non–English-language literature did not yield sufficient high-quality information to justify the resources required for translation.

- MEDLINE® (January 1, 1990, to present)
- EMBASE® (January 1, 1990, to present)
- Cochrane Controlled Trials Register (no date restriction)

To identify systematic reviews, we will search MEDLINE®, the Cochrane Database of Systematic Reviews, the Web sites of the National Institute for Clinical Excellence and the NHA Health Technology Assessment Programme, and Guidelines.gov. We will follow the recommendations of the Agency for Healthcare Research and Quality in its *Methods Guide* about inclusion of results from previously conducted meta-analyses and systematic reviews.[33]

Our search strategy will use the National Library of Medicine's Medical Subject Headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. The searches will be limited to human studies.

We will search MEDLINE for randomized controlled trials, nonrandomized comparative studies, and case series by using the following string of search terms:

> Methicillin-Resistant Staphylococcus aureus" [Mesh] OR ("Methicillin Resistance"[Mesh] AND "Staphylococcus aureus"[Mesh]) OR "methicillin-resistant staphylococcus aureus" OR MRSA AND "prevention and control "[Subheading] OR "Mass Screening"[Mesh] OR screening OR screened OR screen OR surveillance OR diagnosis AND randomized controlled trial [pt] OR controlled clinical trial [pt] OR

randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR "clinical trial" OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR placebos [mh] OR placebo* OR random* OR research design [mh:noexp] OR follow-up studies [mh] OR prospective studies [mh] OR prospectiv* OR volunteer*) OR "Comparative Study "[Publication Type] OR "Evaluation Studies "[Publication Type] OR control OR controlled OR controls.

We will search EMBASE® for randomized controlled trials, nonrandomized comparative studies, and case series by using the following string of search terms:

> 'methicillin-resistant staphylococcus aureus'/exp OR ('methicillin resistance'/exp AND 'staphylococcus aureus'/exp) OR MRSA AND [humans]/lim AND 'prevention and control'/exp OR 'mass screening'/exp OR 'screening'/exp OR screened OR screen OR surveillance OR 'diagnosis'/exp AND [humans]/lim AND 'randomized controlled trial'/exp OR 'randomised controlled trial'/exp OR 'controlled clinical trial'/exp OR 'clinical trial'/exp OR (singl* OR doubl* OR trebl* OR tripl* AND (mask* OR blind*)) OR placebo* OR random* OR 'follow-up study'/exp OR 'prospective study'/exp OR prospectiv* OR volunteer* OR 'comparative study'/exp OR 'evaluation study' OR 'control'/exp OR controlled OR controls AND [humans]/lim.

We will search the Cochrane Controlled Trials Register by using the same search terms used for the MEDLINE and EMBASE searches.

We will also search indexed, electronically searchable conference abstracts by subject heading for the conferences of the following professional societies from the past 5 years: ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy), the Infectious Disease Society of America, the Society for Healthcare Epidemiology of America, the Association of Professionals in Infection Control and Epidemiology, the American College of Physicians, the Pediatric Infectious Diseases Society, the European Society of Clinical Microbiology and Infectious Diseases, the International Society of Infectious Diseases, the European Society of Infectious Diseases, the British Society of Infectious Diseases, the Australasian Society of Infectious Diseases, the International Sepsis Forum, and the European Society of Intensive Care Medicine.

We will review Scientific Information Packets from the Scientific Resource Center and gray literature from the U.S. Food and Drug Administration Web site and ClinicalTrials.gov. We will include those studies that have gone through a process equivalent to journal peer review.
The Technical Expert Panel and individuals and organizations providing peer review will be asked to inform the project team of any studies relevant to the Key Questions that were not included in the draft list of selected studies.

Search results will be stored in an EndNote9® or ProCite® database. Using the study-selection criteria to screen titles and abstracts, a single reviewer will mark each citation as: 1) eligible for review as a full-text article; 2) ineligible for full-text review; or 3) uncertain. Citations marked as uncertain will be reviewed by a second reviewer and resolved by consensus opinion; if necessary, discordant opinions will be resolved by a third reviewer. Using the final study-selection criteria, full-text articles will be reviewed in the same manner to determine inclusion in the systematic review. Records of the reason for exclusion for each paper retrieved in full-text, but excluded from the review, will be kept in the EndNote9 or ProCite database.

C. Data Abstraction and Data Management

- **Data elements.** The following data elements will be abstracted, or recorded as not reported, from intervention studies. Data elements to be abstracted will include the following:

  - Quality Assessment:

    – Number of participants and flow of participants through the steps of the study
    – Treatment allocation methods (including concealment)
    – Use of blinding
    – Prospective versus retrospective
    – Use of an independent outcome assessor
    – Additional elements are described below under Assessment of Methodological Quality of Individual Studies

  - Assessment of Applicability and Clinical Diversity:

    – Patient characteristics, including:

      - Age
      - Sex
      - Race/ethnicity
      - Disease and type
      - Disease duration
      - Other prognostic characteristics (e.g., comorbidities and other potential confounders and/or effect modifiers)
      - Setting

        - Outpatient
        - Inpatient

    – Diagnostic and treatment characteristics, including:

      - Type of assay used to screen for MRSA and its turnaround time
      - Decisionmaking for diagnosis and/or treatment
      - Antibiotic usage
      - Other treatment modalities
      - Duration of observation

  - Outcome Assessment:

    – Identified primary outcome
    – Identified secondary outcomes
    – Response criteria
    – Followup frequency and duration
    – Data analysis details:

      - Statistical analyses (statistical test/estimation results)

        - Test used

□ Summary measures
□ Sample variability measures
□ Precision of estimate
□ *p* values

- Regression modeling techniques

  □ Model type
  □ Candidate predictors and methods for identifying candidates
  □ Univariate analysis results
  □ Selected predictors and methods for selecting predictors
  □ Testing of assumptions
  □ Inclusion of interaction terms
  □ Multivariable model results
  □ Discrimination or validation methods and results
  □ Calibration or "goodness-of-fit" results

- The same abstraction tables will be used for comparative and single-arm studies, although some elements may not apply to the latter (e.g., description of control group).

- **Evidence tables.** Templates for evidence tables will be created in Microsoft Access®. One reviewer will perform primary abstraction of all data elements into the evidence tables, and a second reviewer will review the articles and evidence tables for accuracy. Disagreements will be resolved by discussion, and if necessary, by consultation with a third reviewer. When small differences occur in quantitative estimates of data from published figures, the values will be obtained by averaging the estimates of the two reviewers.

D. Assessment of Methodological Quality of Individual Studies

- **Definition of ratings based on criteria.** In adherence with the *Methods Guide*,[33] the general approach to grading individual comparative studies will be that used by the U.S. Preventive Services Task Force.[35] The quality of the abstracted studies and the body of evidence will be assessed by two independent reviewers. Discordant quality assessments will be resolved with input from a third reviewer, if necessary.

- **The quality of studies will be assessed on the basis of the following criteria:**

  ○ Initial assembly of comparable groups: adequate randomization, including concealment and whether potential confounders (e.g., other concomitant care) were distributed equally among groups.
  ○ Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination).
  ○ Important differential loss to followup or overall high loss to followup.
  ○ Measurements: equal, reliable, and valid (includes masking of outcome assessment).
  ○ Clear definition of interventions.
  ○ All important outcomes considered.
  ○ Analysis: adjustment for potential confounders and intention-to-treat analysis.

- The rating of intervention studies encompasses the three quality categories described here.

  - **Good.** Meets all criteria; comparable groups are assembled initially and maintained throughout the study (followup at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is given to confounders in the analysis. In addition, for randomized controlled trials, intention-to-treat analysis is used.
  - **Fair.** Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: In general, comparable groups are assembled initially, but some question remains about whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and are generally applied equally; some, but not all, important outcomes are considered; and some, but not all, potential confounders are accounted for. An intention-to-treat analysis is done for randomized controlled trials.
  - **Poor.** Studies are graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or are not maintained throughout the study; unreliable or invalid measurement instruments are used, or not applied at all, equally among groups (including not masking the outcome assessment); and key confounders are given little or no attention. For randomized controlled trials, intention-to-treat analysis is lacking.

- The quality of included nonrandomized comparative intervention studies will be also assessed based on a selection of items proposed by Deeks and colleagues36 to inform the approach used by the U.S. Preventive Services Task Force,[35] as follows:

  - Was sample definition and selection prospective or retrospective?
  - Were inclusion/exclusion criteria clearly described?
  - Were participants selected to be representative?
  - Was there an attempt to balance groups by design?
  - Were baseline prognostic characteristics clearly described and groups shown to be comparable?
  - Were interventions clearly specified?
  - Were participants in treatment groups recruited within the same time period?
  - Was there an attempt by investigators to allocate participants to treatment groups in an attempt to minimize bias?
  - Were concurrent/concomitant treatments clearly specified and given equally to treatment groups?
  - Were outcome measures clearly valid, reliable, and equally applied to treatment groups?
  - Were outcome assessors blinded?
  - Was the length of followup adequate?
  - Was attrition below an overall high level (<20 percent)?
  - Was the difference in attrition between treatment groups below a high level (<15 percent)?
  - Did the analysis of outcome data incorporate a method for handling confounders such as statistical adjustment?

- The quality of included single-arm intervention studies will be assessed based on a set of study characteristics proposed by Carey and Boden,[37] as follows:
  - Clearly defined question
  - Well-described study population
  - Well-described intervention
  - Use of validated outcome measures
  - Appropriate statistical analyses
  - Well-described results
  - Discussion and conclusion supported by data
  - Funding source acknowledged

E. Data Synthesis

Whether or not this evidence review will incorporate formal data synthesis (by using meta-analysis), will be determined after completing the formal literature search. If a meta-analysis can be performed, subgroup and sensitivity analyses will be based on assessment of clinical diversity in available studies. Anticipated subgroups include patients at high-risk for MRSA, including those with end-stage renal disease and those residing in long-term care facilities. The *Methods Guide*[33] and the paper by Owens and colleagues[38] will be used to rate the strength of the overall body of evidence.

F. Grading the Evidence for Each Key Question

Applicability of findings in this review will be assessed within the EPICOT framework (Evidence, Population, Intervention, Comparison, Outcome, and Timestamp). Selected studies will be assessed for relevance against target populations, interventions of interest, and outcomes of interest. The system used for rating the strength of the overall body of evidence was developed by the Agency for Healthcare Research and Quality for its *Methods Guide*,[33,38] based on a system developed by the GRADE Working Group.[39] This system explicitly addresses the following domains: risk of bias, consistency, directness, and precision. The grade of evidence strength is classified into the following four categories:

- **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 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 effect and is likely to change the estimate.
- **Insufficient.** Evidence is either unavailable or does not permit estimation of an effect.

Additional domains will be addressed—such as strength of association, publication bias, coherence, and dose-response relationship—and residual confounding will be assessed if appropriate.

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VI. Definition of Terms

None.

VII. Summary of Protocol Amendments

Section	Original Protocol	Revised Protocol	Rationale
IV. Methods A. Criteria for Inclusion/ Exclusion of Studies in the Review	We will include randomized, controlled studies and nonrandomized, comparative studies (observational, case-control, and cohort studies) of populations, comparisons, interventions, and outcomes that were not adequately studied in controlled trials. We will also use observational studies to assess comparative effectiveness in populations not well represented in randomized controlled trials. To classify	We will include randomized, controlled studies and nonrandomized, comparative studies (observational, case-control, and cohort studies) of populations, comparisons, interventions, and outcomes that were not adequately studied in controlled trials. We will also use observational studies to assess comparative effectiveness in populations not well represented in randomized controlled trials. To classify observational study designs, we will use the system developed by Briss and colleagues.[34] Studies will be included	We desired a clearer description and refinement of study eligibility criteria.

	observational study designs, we will use the system developed by Briss and colleagues.[34]	that have these design characteristics and meet descriptions included under Population(s), Interventions, Comparators, Outcomes, Timing and Settings. Additionally, studies will be excluded that: 1) do not describe any statistical analysis; or 2) report a relevant outcome only as a frequency without a denominator.	
IV. Methods B. Searching for the Evidence	Search results will be stored in an EndNote9® or ProCite® database. Using the study-selection criteria to screen titles and abstracts, a single reviewer will mark each citation as: 1) eligible for review as a full-text article; 2) ineligible for full-text review; or 3) uncertain. Citations marked as uncertain will be reviewed by a second reviewer and resolved by consensus opinion; if necessary, discordant opinions will be resolved by a third reviewer. Using the final study-selection criteria, full-text articles will be reviewed in the same manner to determine inclusion in the systematic review. Records of the reason for exclusion for each paper retrieved in full-text, but	In the course of this project, our EPC anticipates transition from EndNote® or ProCite® databases to use of Distiller SR®. Therefore, search results will initially be stored in an EndNote9® or ProCite® database, subsequently there will be a transfer of data to Distiller SR®. In an initial screen of titles and abstracts, study-selection criteria will be applied by a single reviewer who will mark each citation as: 1) eligible for review as a full-text article; 2) ineligible for full-text review; or 3) uncertain. Citations marked as uncertain will be reviewed by a second reviewer and resolved by consensus opinion; and when necessary, discordant opinions will be resolved by a third reviewer. Throughout the title/abstract screening and study selection processes, there will be reviewer training and quality control procedures to achieve accuracy. Final	In the course of this project, we transitioned to use of Distiller SR**®** software and implemented enhanced quality control procedures to reduce chances of missing relevant studies that should be included in this comparative effectiveness review.

	excluded from the review, will be kept in the EndNote9 or ProCite database.	study-selection criteria will be applied to full-text articles in the same manner to determine inclusion in the systematic review. Records of the reason for exclusion for each paper retrieved in full-text, but excluded from the review, will be kept in the EndNote9 and Distiller SR® databases. Forms to facilitate title and abstract review and full text screening will be pilot tested during reviewer training.	
IV. Methods C. Data Abstraction and Data Management	**Data elements.** The following data elements will be abstracted, or recorded as not reported, from intervention studies. Data elements to be abstracted will include the following:	**Data elements.** Using Distiller SR® software, the following data elements will be abstracted, or recorded as not reported, from intervention studies. Data elements to be abstracted will include the following:	We wish to acknowledge that we are using a new software solution for data abstraction.
IV. Methods C. Data Abstraction and Data Management	**Evidence tables.** Templates for evidence tables will be created in Microsoft Access®. One reviewer will perform primary abstraction of all data elements into the evidence tables, and a second reviewer will review the articles and evidence tables for accuracy. Disagreements will be resolved by discussion, and if necessary, by consultation with a third reviewer. When small differences occur in quantitative estimates of data from published figures, the values will be obtained by averaging the estimates of the two reviewers.	**Evidence tables.** Templates for evidence tables will be created in Microsoft Excel® and Microsoft Word® after data is downloaded from Distiller SR®. Forms to facilitate data abstraction will be pilot tested during implementation of quality control to achieve accuracy. One reviewer will perform primary abstraction of all data elements into the evidence tables, and a second reviewer will review the articles and evidence tables for accuracy. Disagreements will be resolved by discussion, and if necessary, by consultation with a third reviewer. When small differences occur in quantitative estimates of data from published figures, the values will be obtained by averaging the estimates of the two reviewers.	We wish to acknowledge that we are using a new software solution for data abstraction and creation of evidence tables.

IV. Methods D. Assessment of Methodological Quality	**Definition of ratings based on criteria.** In adherence with the *Methods Guide*,33 the general approach to grading individual comparative studies will be that used by the U.S. Preventive Services Task Force.35 The quality of the abstracted studies and the body of evidence will be assessed by two independent reviewers. Discordant quality assessments will be resolved with input from a third reviewer, if necessary.	**Definition of ratings based on criteria.** In adherence with the *Methods Guide*,33 the general approach to grading individual comparative studies will be that used by the U.S. Preventive Services Task Force.35 According to this approvch, studies lacking control for confounding would be considered fatally flawed and therefore of poor quality. Therefore, full assessment of study quality will be performed for only those studies that utilize statistical methodologies to explicitly account for confounding. The quality of the abstracted studies and the body of evidence will be assessed by two independent reviewers. Discordant quality assessments will be resolved with input from a third reviewer, if necessary.	Complete assessment of quality for those studies lacking control for confounding would not provide meaningful additional information given that these studies are fatally flawed by definition of the rating system we used.We plan to focus this comparative effectiveness review on the higher quality evidence.

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 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.