Effective Health Care

Acute Kidney Injury

Results of Topic Selection Process

- The topic, *Acute Kidney Injury*, will go forward for refinement as a systematic review. The scope of this topic, including populations, interventions, comparators, and outcomes, will be further developed in the systematic review.

- Amendment (September 2016): Due to limited program resources, the program is unable to develop a review at this time. No further activity on this topic will be undertaken by the Effective Health Care (EHC) Program.

Nomination

Topic Number: 0661 **Received On:** 11/12/2015

Topic Name: Acute Kidney Injury

Nominator: A medical officer at the Center for Medicare and Medicaid Services (CMS), Quality Improvement Group in the Division of ESRD Population and Community Health (EPCH).

Nomination Summary: The nominator is interested in identifying best practices for patients with acute kidney injury (AKI-D) receiving renal replacement therapies in outpatient settings. Due to a policy change that will go into effect in January 2017 which will allow for the reimbursement of outpatient renal replacement therapies for individuals with AKI-D, CMS is interested in a systematic review to help guide policies and clinical practice for this population. In addition, currently no standardized predictive analytic tools based on diagnostic tests or clinical comorbidities to predict which AKI-D patients will recover renal function and which will regress to irreversible loss of renal function and require continued dialysis exist. The nominator hopes that an AHRQ systematic review will identify knowledge gaps and inform research priorities for the AKI population.

Key Questions from Nomination:

Key Question 1: “For patients with a diagnosis of Acute Kidney Injury (AKI) who continue to require dialysis upon hospital discharge, what is the comparative effectiveness of different treatment strategies for treating clinical features of AKI? Specifically, are certain strategies more likely to expedite renal recovery, improve quality of life, and reduce mortality? For instance, what are the comparative effectiveness, [and] risks and benefits of different strategies for managing: fluid volume, blood pressure, anemia, nutrition, and bone mineral disease?”

Key Question 2: “Is there an optimal dialysis modality (peritoneal vs. intermittent hemodialysis vs. continuous renal replacement therapy), length, or frequency of dialysis in this population with respect to expediting renal recovery, improving quality of life, and reducing mortality?”

Key Question 3: “What are early and late predictors that renal function will not recover in patients with AKI requiring dialysis, and how can these be used to inform optimal timing of arteriovenous fistula and graft placement as well as kidney transplantation?”

Key Question 4: “What is the optimal frequency of laboratory monitoring and clinical assessment of patients with AKI requiring outpatient dialysis for identifying renal recovery and managing complications of AKI? How does this differ from patients with end-stage renal disease (ESRD)?”

Revised Key Questions: Due to a paucity of research examining individuals with Acute Kidney Injury requiring dialysis (AKI-D) receiving renal replacement therapy in outpatient settings, we have revised the key questions to include studies examining hospitalized patients with AKI-D, a population that has been better studied. Evidence from this population may provide relevant evidence related to the questions of interest. However, it is important to note that interventions and outcomes (e.g., renal recovery) in research focused on individuals in intensive and critical care settings with AKI-D may differ from those that might be the focus for outpatients; thus, applicability to the population of interest may be limited.

Key Question 1: For individuals with a diagnosis of acute kidney injury requiring dialysis (AKI-D), are certain treatment strategies for the clinical features of AKI (e.g., fluid volume, blood pressure, anemia, nutrition, and bone mineral disease) more likely to result in improved outcomes?

a. What are the associated benefits, such as renal recovery, quality of life, and mortality?
b. What are the associated harms and costs?

Key Question 2: For individuals with AKI-D, what are the optimal renal replacement modalities (including frequency) for outcomes?

a. What are the associated benefits, such as renal recovery, quality of life, and mortality:
    i. Of hemofiltration (HF) and/or hemodialysis (HD) approaches for continuous renal replacement therapies (CRRTs)?
    ii. Of continuous versus intermittent or extended daily hemofiltration and/or hemodialysis?
    iii. Of peritoneal dialysis (PD) modalities or compared to hemofiltration and/or hemodialysis?
b. What are the associated harms and costs:
    i. Of hemofiltration (HF) and/or hemodialysis (HD) approaches for continuous renal replacement therapies (CRRTs)?
    ii. Of continuous versus intermittent or extended daily hemofiltration and/or hemodialysis?
    iii. Of peritoneal dialysis (PD) modalities or compared to hemofiltration and/or hemodialysis?

Key Question 3: For outcomes such as renal recovery, quality of life, and mortality for individuals with AKI-D, what is the effect of:

a. Dose?
b. Timing/initiation?
c. Fluid Composition?
d. Session time/length?

Key Question 4: What are early and late predictors of renal function non-recovery and mortality in individuals with AKI-D?

Key Question 5: For laboratory monitoring and clinical assessment of individuals with AKI-D:

a. What are the optimal frequency and parameters to mitigate renal non-recovery and complications of AKI-D or associated treatments?
b. How do the frequency or parameters for individuals with AKI-D differ from those with end-stage renal disease (ESRD)?

Policy and/or Clinical Context from the Nomination:

- "According to a recently published article, about 20% of hospitalized patients develop AKI, and of that 20%, 1-2% requires dialysis. Of these individuals requiring dialysis, 10-30% requires dialysis after hospital discharge. 20-50% of this population recovers renal function within 90 days. The rest are typically diagnosed with ESRD after 90 days. (Cerda et al., CJASN 2015)."
- "AKI-D is increasingly common among hospitalized patients. Not infrequently, patients with AKI-D do not experience renal recovery prior to hospital discharge. When these patients are ready for hospital discharge, providers must arrange for continued dialysis, which can be done in one of three ways: 1) The patients can remain hospitalized until renal function has recovered; 2) They can receive dialysis in a hospital outpatient setting, or; 3) They can receive dialysis at ESRD facilities."
- "In June 2015, the U.S. Congress amended Section 1861(s)(2)(F) of the Social Security Act by allowing payment for renal dialysis services furnished at outpatient dialysis facilities for persons with AKI beginning on or after January 1, 2017. This makes Medicare payment consistent with many private insurers, which generally reimburse for outpatient dialysis in patients with AKI in ESRD facilities."
- "Lack of renal function recovery after 90 days is generally accepted as meeting criteria for ESRD, though some may be diagnosed with ESRD earlier based on risk factors including pre-existing chronic kidney disease (CKD), old age, and other comorbidities. Of concern is that individuals with AKI may be inappropriately perceived and managed as having ESRD which could potentially delay renal recovery. For example, an approach to fluid removal consistent with ESRD management may result in episodes of hypotension due to hypovolemia, and could potentially delay or prevent renal function recovery. (Heung et al., CJASN 2015)."
- "As more dialysis for patients with AKI-D is performed in outpatient ESRD facilities due to changes in payment policies, it is increasingly important to understand whether, and how, care for these patients should differ from care for patients with ESRD. Similar to patients with ESRD, patients with AKI-D are at a high risk for death and other health complications. However, they differ from patients with ESRD because their renal function often times recovers; thus they may require closer monitoring to identify improvements in renal function, and to determine if and when dialysis can be discontinued. It is unknown how outpatient dialysis care for patients with AKI-D should differ from outpatient dialysis care for patients with ESRD."
- "There are no standardized predictive analytic tools based on diagnostic tests or clinical comorbidities to predict which AKI patients will recover renal function and which will regress to irreversible loss of renal function and require continued dialysis."

Effective Health Care

Acute Kidney Injury

Topic #: 0661

Nomination Date: 11/12/2015

Topic Brief Date: March 2016

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary of Key Findings from the Topic Brief:

A new evidence review examining interventions for individuals with acute kidney injury requiring dialysis (AKI-D) is both appropriate and important. Approximately 10-30% of patients that survive in-hospital AKI-D require renal replacement therapy post-discharge. However, there are currently no established guidelines for the treatment of AKI-D in outpatient settings. The uncertainty around care for individuals with AKI-D in outpatient settings, combined with the upcoming change in CMS reimbursement policies result in the potential for a new AHRQ evidence review to make a significant impact.

There is little direct evidence related to the treatment of individuals with AKI-D in outpatient settings, as the bulk of the existing research examines patients in intensive or critical care units. However, a new AHRQ systematic review does have value. Until there is established research examining individuals with AKI-D in outpatient settings, a synthesis of the relevant indirect evidence has the potential to impact clinical decision-making and inform policy.

The nominator is aware of the paucity of research examining AKI-D in outpatient settings, as well as the potential for limited applicability to the population of interest. However, given the need to determine best practices and establish policies and the lack of existing evidence and guidance specific to this population, the nominator is interested in a systematic review of the existing relevant literature.

There are a number of existing and in-process systematic reviews examining the benefits and harms associated with different renal replacement modalities, as well as variables related to dose, timing/initiation of renal replacement therapy, and fluid composition. However, a new evidence review covering both the scope needed by the nominator to inform CMS policies, and focused on the populations and outcomes most applicable to individuals with AKI-D in outpatient settings in the United States would not be duplicative. Original research related to some of the key questions of interest may be limited; however, a new evidence review will serve not only to guide clinical decision-making and policy, and particularly relevant for this patient population, identify research gaps and inform future research.

- Key Question 1a. Benefits of treatment strategies for the clinical features of AKI
    - A new evidence review *would not be duplicative*. We identified no completed or in-process evidence reviews examining benefits for the clinical features of AKI.
    - From the 200 randomly selected studies we examined, we identified no studies covering the scope of the key question.
- Key Question 1b. Harms and costs of treatment strategies for the clinical features of AKI
    - A new evidence review *would not be duplicative*. We identified no completed or in-process evidence reviews covering the scope of the key question.
    - From the 200 randomly selected studies we examined, we identified no studies examining benefits for the clinical features of AKI.
- Key Question 2a. Benefits of Renal Replacement Modalities
    - 2.a.i. Among hemofiltration and/or hemodialysis continuous renal replacement therapies
        - A new evidence *would be duplicative*. We identified a 2012 meta-analysis, comparing hemofiltration to hemodialysis. All studies included ICU patients, and the review examined mortality, dialysis dependence, filter life and organ dysfunction, and other clinical outcomes.
        - One of the 200 randomly selected studies we examined continuous renal replacement therapies (CRRT), for an expected total of four studies.
    - 2.a.ii. Continuous versus extended daily or intermittent hemofiltration and/or hemodialysis
        - A new evidence review *would be duplicative*. We identified a 2015 and a 2013 review comparing CRRTs to extended daily dialysis (EDD) or intermittent hemodialysis (IHD) on mortality, kidney recovery, dialysis dependence, and fluid removal.
        - From the randomly selected 200 studies we examined, three comparing continuous, extended daily, and IHD, for an expected total of 11 studies.
    - 2.a.iii. Among peritoneal dialysis modalities or compared to hemofiltration and/or hemodialysis
        - A new evidence review *would be duplicative*. We identified a 2012 Cochrane review, a 2013 review, and a Cochrane protocol (anticipated completion date February 2017) examining PD alone or as compared to HD. While the Cochrane review includes only one study comparing PD to continuous equilibrating peritoneal dialysis (CEPD), and the 2013 review, which compares PD to CRRT, IHD, and daily hemodialysis (DHD), only examines mortality, the in-process review will include studies comparing PD with and without supportive treatment to HD (including all different modalities of IHD or CRRT) with and without supportive treatment, as well as different modalities of PD on outcomes such as kidney function, duration of renal replacement therapy and laboratory indices.

        - From the randomly selected 200 studies we examined, two examined harms or costs associated with PD or as compared to HD, for an expected total of 8 studies.
- Key Question 2b. Harms and Costs of Renal Replacement Modalities
    - 2.b.i. Among hemofiltration and/or hemodialysis continuous renal replacement therapies
        - A new evidence *would not be duplicative*. We identified a 2012 meta-analysis, comparing hemofiltration to hemodialysis on organ dysfunction and filter failure among ICU patients. No other harms were examined. We identified no reviews examining costs.
        - From the 200 randomly selected studies we examined, we identified no examining harms or costs associated with CRRT.
    - 2.b.ii. Continuous versus extended daily or intermittent hemofiltration and/or hemodialysis
        - A new evidence *would not be duplicative*. We identified one review comparing EDD to CRRT on episodes of vasopressure escalation and cost. No other harms were examined.
        - From the randomly selected 200 studies we examined, four compared harms or costs associated with continuous, extended daily, or intermittent HD, for an expected total of 14 studies.
    - 2.b.iii. Among peritoneal dialysis modalities or compared to hemofiltration and/or hemodialysis
        - A new evidence review *would be duplicative*. We identified a 2013 Cochrane review, a 2013 review, and an in-process Cochrane review (anticipated completion date February 2017) examining PD alone or as compared to HD. Although the existing review includes only one study comparing PD to CEPD on time and cost, the in-process review will include studies comparing PD with and without supportive treatment to HD (including all different modalities of IHD or CRRT) with and without supportive treatment, as well as different modalities of PD on outcomes related to cost, and adverse events such as including bleeding, peritonitis, respiratory insufficiency, and hypoalbuminemia.
        - From the 200 randomly selected studies we examined, we identified no studies examining harms or costs associated with PD or as compared to HD.
- Key Question 3a. RRT Dose
    - A new evidence review *would not be duplicative*. We identified a 2011 evidence review comparing high to low intensity CRRT in critically ill patients. No other outcomes were examined
    - From the 200 randomly selected studies we examined, we identified three studies examining dose, for an expected total of 11 studies.
- Key Question 3b. Timing/Initiation of RRT
    - A new evidence review *would likely be duplicative*. We identified three completed reviews examining timing/initiation, with congruent findings examining the topic.
    - One of the 200 randomly selected studies we examined related to the timing/initiation of renal replacement therapy, for an expected total of four studies.
- Key Question 3c. Fluid Composition
    - A new evidence review comparing bicarbonate vs. lactate-buffered fluids *would be duplicative*. We identified both a 2015 Cochrane and another (2014) review

comparing bicarbonate to lactate-buffered solutions on outcomes such as serum creatinine, hypotensive episodes, and mortality. (Table 6). However, a new review examining anticoagulants *would not be duplicative*. We identified no completed or in-process reviews.
    - From the 200 randomly selected studies we examined, we identified three studies examining fluid composition, for an expected total of 11 studies.
- Key Question 3d. Time/Length of RRT Session
    - A new evidence review *would not be duplicative*. We identified no completed or in-process reviews covering the scope of the key question.
    - One of the 200 randomly selected studies we examined related to time/length of RRT session, for an expected total of four studies.
- Key Question 4. Predictors of Renal Outcomes and Mortality
    - A new evidence review *would not be duplicative*. We identified no relevant completed or in-process evidence reviews.
    - We identified seven studies related to predictors, from the randomly selected 200 we examined, for an expected total of 25 relevant studies.
- Key Question 5a. Optimal Frequency/Parameters of Laboratory Monitoring and Clinical Assessment
    - A new evidence review *would not be duplicative*. We identified no relevant completed or in-process reviews.
    - From the 200 randomly selected studies we examined, we identified two studies examining optimal frequency/parameters for an expected total of seven relevant studies.
- Key Question 5b. Comparing AKI-D to End Stage Renal Disease (ESRD) on Optimal Frequency/Parameters of Laboratory Monitoring and Clinical Assessment
    - A new evidence review *would not be duplicative*. We identified no relevant completed or in-process reviews comparing individuals with AKI-D to individuals with ESRD on optimal frequency/parameters.
    - From the 200 randomly selected studies we examined, no studies compared individuals with AKI-D to individuals with ESRD on optimal frequency/parameters.

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NOTE: The purpose of the topic selection process for the Agency for Healthcare Research and Quality's (AHRQ) Effective Healthcare Program (EHC) is the prioritization of nominations for systematic reviews and other AHRQ EHC reports. This topic brief is not, nor is it intended as a systematic review of the topic.

Introduction

Acute kidney injury (AKI) is an abrupt decline in the glomerular filtration rate that results in increases in serum levels of metabolic waste products normally excreted by the kidney. AKI is common in hospitalized patients, many of whom have exposures (for example, to medications or contrast dye) or conditions (e.g., sepsis, hypotension) that predispose to AKI. Management of AKI is supportive and is aimed at avoiding continuing or new insults to the kidney, including:

- discontinuation of medications that may have caused AKI
- volume replacement if depletion is suspected
- avoidance and treatment of fluid overload and of electrolyte disturbances associated with renal failure, such as hyperkalemia, hypocalcemia, and hyperphosphatemia.

Most patients with AKI recover before they have indications for renal replacement therapy. Renal replacement therapy is used when fluid overload, electrolyte disturbances, metabolic acidosis cannot be controlled with medications; when signs and symptoms of uremia develop; or when a prolonged course of recovery is anticipated.

There are a number of different renal replacement therapy modalities, including hemodialysis (HD), peritoneal dialysis (PD), hemofiltration, and hemodiafiltration (hemofiltration plus hemodialysis). Hemodialysis, hemofiltration, and hemodiafiltration are commonly used in the United States, can use an arteriovenous or veno-venous route, and the frequency can vary. Continuous renal replacement therapies (CRRTs) are typically administered in intensive care settings, and include continuous hemodialysis (CHD; i.e., continuous arteriovenous hemodialysis [CAVHD] and continuous veno-venous hemodialysis [CVVHD]), continuous hemofiltration (CHF; i.e., continuous artero-venous hemofiltration [CAVHF] and continuous veno-venous hemofiltration [CVVHF]), and continuous hemodiafiltration (CHDF; i.e., continuous arteriovenous hemodiafiltration [CAVHDF] and continuous veno-venous hemodiafiltration [CVVHDF]). Renal replacement therapies can also be administered less frequently, and include intermittent hemodialysis (IHD), as well as prolonged intermittent renal replacement therapies (PIRRTs) such as extended daily [hemo]dialysis (EDD) and sustained low efficiency dialysis (SLED).

According to the AKI Advisory Group of the American Society of Nephrology, "[Acute Kidney Injury requiring Dialysis] (AKI-D) has traditionally been considered a problem of acute care management focused on hospital survival, but minimal attention has been paid to measures to promote kidney function recovery."[1]

Topic nomination #0661, *Acute Kidney Injury*, was received on November 12, 2015, and was nominated by an individual identifying themselves as a medical officer at the Center for Medicare and Medicaid Services, Quality Improvement Group in the Division of ESRD [End-Stage Renal Disease] Population and Community Health (EPCH). The key questions for this nomination are as follows:

Key Question 1: For individuals with a diagnosis of Acute Kidney Injury requiring dialysis (AKI-D), are certain treatment strategies for the clinical features of AKI (e.g., fluid volume, blood pressure, anemia, nutrition, and bone mineral disease) more likely to result in improved outcomes?

a. What are the associated benefits, such as renal recovery, quality of life, and mortality?
b. What are the associated harms and costs?

Key Question 2: For individuals with AKI-D, what are the optimal renal replacement modalities (including frequency) for outcomes?

a. What are the associated benefits, such as renal recovery, quality of life, and mortality:
    i. Of hemofiltration (HF) and/or hemodialysis (HD) approaches for continuous renal replacement therapies (CRRTs)?
    ii. Of continuous versus intermittent or extended daily hemofiltration and/or hemodialysis?
    iii. Of peritoneal dialysis (PD) modalities or compared to hemofiltration and/or hemodialysis?
b. What are the associated harms and costs:
    i. Of hemofiltration (HF) and/or hemodialysis (HD) approaches for continuous renal replacement therapies (CRRTs)?
    ii. Of continuous versus intermittent or extended daily hemofiltration and/or hemodialysis?
    iii. Of peritoneal dialysis (PD) modalities or compared to hemofiltration and/or hemodialysis?

Key Question 3: For outcomes such as renal recovery, quality of life, and mortality for individuals with AKI-D, what is the effect of:

a. Dose?
b. Timing/initiation?
c. Fluid Composition?
d. Session time/length?

Key Question 4: What are early and late predictors of renal function non-recovery and mortality in individuals with AKI-D?

Key Question 5: For laboratory monitoring and clinical assessment of individuals with AKI-D:

a. What are the optimal frequency and parameters to mitigate renal non-recovery and complications of AKI-D or associated treatments?
b. How do the frequency or parameters for individuals with AKI-D differ from those with end-stage renal disease (ESRD)?

Our approach was guided by an analytic framework (see Figure 1) and informed by discussions with two nephrologists. In addition, to define the inclusion criteria for the key questions, we specify the population, interventions, comparators, outcomes, timing, and setting (PICOTS) of interest. PICOTS are outlined in Table 1.

Figure 1. Analytical Framework

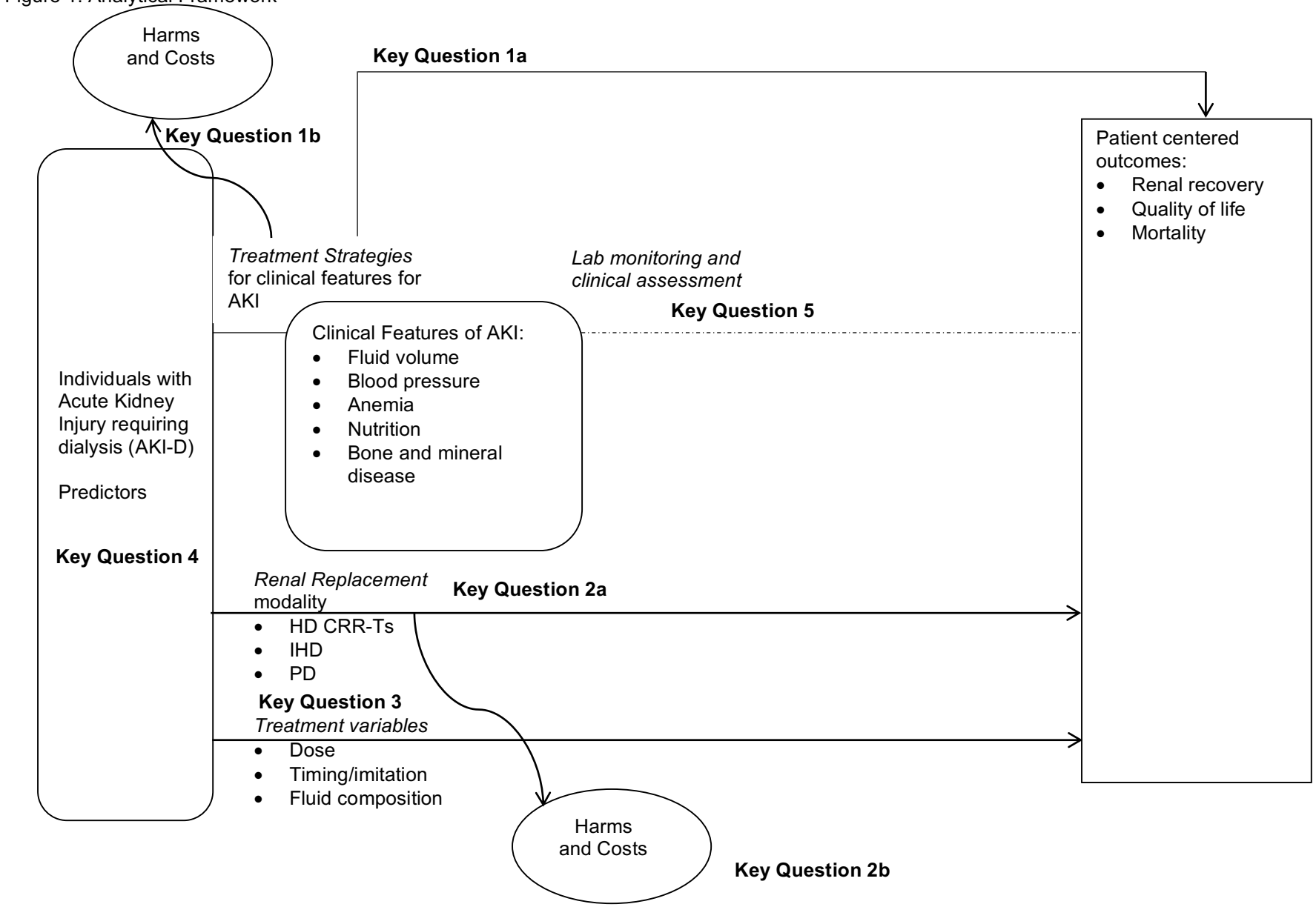


Table 1. PICOTS by Key Question

Key Questions	**KQ1.** For individuals with a diagnosis of Acute Kidney Injury requiring dialysis (AKI-D), are certain treatment strategies for the clinical features of AKI (e.g., fluid volume, blood pressure, anemia, nutrition, and bone mineral disease) more likely to result in improved outcomes? a. What are the associated benefits, such as renal recovery, quality of life, and mortality? b. What are the associated harms and costs?	**KQ2.** For individuals with AKI-D, what are the optimal renal replacement modalities (including frequency) for outcomes ? a. What are the associated benefits? b. What are the associated harms and costs?	**KQ3.** For outcomes such as renal recovery, quality of life, and mortality for individuals with AKI-D, what is the effect of: a. Dose? b. Timing/initiation? c. Fluid Composition? d. Session Time/Length?	**KQ4.** What are early and late predictors of renal function non-recovery and mortality in individuals with AKI-D?	**KQ 5.** For laboratory monitoring and clinical assessment of individuals with AKI-D: a. What are the optimal frequency and parameters to mitigate renal non-recovery and complications of AKI-D or associated treatments? b. How do the frequency or parameters for individuals with AKI-D differ from those with ESRD?
Population	Individuals with AKI-D	Individuals with AKI-D	Individuals with AKI-D	Individuals with AKI-D	AKI-D and ESRD patients
Interventions	Treatment strategies for treating clinical features of AKI: fluid volume, blood pressure, anemia, nutrition, and bone mineral disease.	Renal replacement therapy modalities (e.g., PD, IHD, IRRT, CRRT, SLED, EDD)	Timing, dose, fluid composition, length	NA	Clinical assessments and laboratory monitoring.
Comparators	Other active treatment, usual care	Other active treatment, usual care	Other active treatment, usual care	Other active treatment, usual care, or no comparator	Other active monitoring, usual care
Outcomes	Renal recovery, quality of life, mortality. Harms (e.g., hypotension, cardiovascular events, etc.)	Renal recovery, quality of life, mortality. Harms (e.g., hypotension, cardiovascular events, etc.)	Renal recovery, quality of life, mortality. Harms (e.g., hypotension, cardiovascular events, etc.)	Lack of renal recovery	Renal recovery and complications, mortality
Timing	No restrictions	No restrictions	No restrictions	No restrictions	No restrictions
Setting	Inpatient and Outpatient settings	Inpatient and Outpatient settings	Inpatient and Outpatient settings	Inpatient and Outpatient settings	Inpatient and Outpatient settings

Abbreviations: AKI-D=Acute Kidney Injury-Dialysis; CRRT=Continuous Renal Replacement Therapy; EDD=Extended Daily Dialysis; ESRD=End Stage Renal Disease; IHD=Intermittent Hemodialysis; IRRT=Intermittent Renal Replacement Therapy; PD=Peritoneal Dialysis; SLED=Sustained Low-Efficiency dialysis

Methods

To assess topic nomination #0661, *Acute Kidney Injury*, for priority for a systematic review or other AHRQ EHC report, we used a modified process based on established criteria. Our assessment is hierarchical in nature, with the findings of our assessment determining the need for further evaluation. Details related to our assessment are provided in Appendix A.

1. Determine the appropriateness of the nominated topic for inclusion in the EHC program.
2. Establish the overall importance of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the desirability of a new evidence review by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the potential impact a new systematic review or other AHRQ product.
5. Assess whether the current state of the evidence allows for a systematic review or other AHRQ product (feasibility).
6. Determine the potential value of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance (see Appendix A).

Desirability of a New Evidence Review/Duplication

To assess the desirability of new research/duplication, we conducted a search for existing or in progress high quality systematic reviews. We searched the following organizations/websites: Agency for Healthcare Research and Quality (AHRQ), Veterans Administration (VA), Cochrane Systematic Reviews and Protocols, UK National Health Service, PubMed/MEDLINE, Health Technology Assessment (HTA), and PROSPERO.

The search for duplication for topic nomination #0661, Acute Kidney Injury, was conducted on January 8, 2016 and covered the period from January 2011 to January 2016.

Impact of a New Evidence Review

We reviewed whether a new evidence review could potentially impact the standard of care or resolve practice variation (see Appendix A).

Available Primary Research for an Evidence Review

Literature Search. To assess the volume of literature and the size of a potential systematic review, a research librarian created search strategy designed to address the key questions in the nomination (see Appendix B). We conducted a literature search of PubMed/MEDLINE covering January 2007 to January 2016. Using established PubMed/MEDLINE filters, we categorized studies as randomized controlled trials,[2] systematic reviews,[3] and other. For searches identifying greater than 200 unique titles, we randomly selected a total of 200 articles to review and calculated the percent included and the expected total included for the total yield and each of the three independent categories.

Study Selection. We developed criteria for population, interventions, comparators, outcomes, timing, and study design (PICOTS) as criteria for inclusion/exclusion (see Table 1). One investigator reviewed the titles and abstracts.

Clinical Trials. We searched ClinicalTrials.gov for open studies relevant to the key questions in this nomination.

Value

We evaluated whether the proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change and whether the review has the potential to influence practice (see Appendix A).

Clinical Consultation

We consulted a nephrologist to provide relevant clinical context to assist with the revision of key questions and the development of PICOTS. A second nephrologist provided feedback of the draft brief and the organization of the key questions.

Stakeholder Discussion and Feedback

We engaged the nominator in a discussion after the initial revision of the key questions and development of PICOTS, and continued to seek and receive feedback when questions arose throughout the process. The nominator is aware of the paucity of research examining AKI-D in outpatient settings, as well as the potential for limited applicability to the population of interest. However, given upcoming changes in policy allowing for Centers for Medicare & Medicaid Services (CMS) reimbursement for individuals with AKI-D in outpatient settings, the nominator is interested in a systematic review of the existing literature that largely examines critically ill individuals with AKI-D to help to inform policies and practice.

Compilation of Findings

We constructed a table outlining the selection guidelines and criteria as they pertain to this nomination. In addition, we also constructed a summary of evidence tables that include the key questions, and the findings of the search for duplication, the literature search, and the search for clinical trials.

Results

Appropriateness and Importance

Acute Kidney Injury is an appropriate and important topic. Acute Kidney Injury requiring renal replacement therapy occurs in 6% of critically ill patients[1] and is associated with a 50% mortality rate in the ICU.[1] Between 10-30% of patients that survive in-hospital AKI-D require renal replacement therapy post-discharge.[4] However, little is known about whether particular management strategies or treatments facilitate renal recovery in AKI-D patients. A clear understanding of the effectiveness and harms associated with treatments for AKI-D would be of interest to clinicians, patients, and payers, especially in light of the 2015 amendment to the

Social Security Act which permits Medicare patients to receive treatment for AKI-D at out-patient dialysis facilities beginning in 2017. See Appendix A for details.

Desirability of a New Evidence Review/Duplication

Our search for duplication from January 2011 to January 2016 resulted in 24 evidence reviews and 1 protocol examining the treatment for patients with AKI-D.

Key Question 1

For individuals with a diagnosis of Acute Kidney Injury requiring dialysis (AKI-D), are certain treatment strategies for the clinical features of AKI-D (e.g., fluid volume, blood pressure, anemia, nutrition, and bone mineral disease) more likely to result in improved outcomes?

Key question 1a. What are the associated benefits, such as renal recovery, quality of life, and mortality?

We identified no evidence reviews examining outcomes related to treatment strategies for the clinical features of AKI-D.

Key question 1b. What are the associated harms and costs?

We identified no evidence reviews examining harms and costs associated with treatment strategies for the clinical features of AKI-D.

Key Question 2

What are the optimal renal replacement modalities (including frequency) for outcomes such as renal recovery, quality of life, and mortality?

We identified five evidence reviews[5-9] and one protocol[10] examining the benefits, harms, and costs related to different renal replacement therapy modalities.

Key question 2.a.i. What are the associated benefits among hemofiltration and/or hemodialysis continuous renal replacement therapies (CRRTs)?

A new evidence review would be duplicative. We identified a 2012 meta-analysis, comparing continuous hemofiltration to hemodialysis.[6] All studies included ICU patients, and the review examined mortality, renal replacement therapy dependence, filter life and organ dysfunction, and other clinical outcomes. Findings indicated no differences in mortality or renal replacement therapy dependence (see Table 2).

Key question 2.a.ii. What are the associated benefits of continuous versus extended daily or intermittent hemofiltration and/or hemodialysis?

A new evidence review would be duplicative. We identified two reviews comparing CRRTs to extended daily or intermittent hemodialysis.[8,9] One review compared extended daily dialysis (EDD) to CRRT on mortality, kidney recovery, ICU days, and fluid removal and found no difference in mortality rate in RCTs and a lower mortality risk associated with EDD in observational studies. There was no difference in kidney recovery rate.[9] A second review compared continuous to intermittent renal replacement therapies. All but one study was

conducted in ICU settings. Findings indicate a higher rate of renal replacement therapy dependence associated with intermittent therapy (see Table 2).[8]

Key question 2.a.iii. What are the associated benefits among peritoneal dialysis (PD) modalities, or PD versus hemofiltration and/or hemodialysis?

A new evidence review would be duplicative. We identified two reviews[5,7] (one Cochrane),[7] and one Cochrane protocol[10] examining peritoneal dialysis alone or compared to hemodialysis. A 2012 Cochrane review compared tidal PD to other forms of PD. The review included only one study, which compared tidal PD to continuous equilibrating PD (CEPD) and determined that there was insufficient evidence from which to form conclusions.[7] A second review compared PD to various forms of HD, and found no difference in mortality (see Table 2).[5]

The in-process Cochrane review will compare PD with and without supportive treatment with HD (including all different modalities of IHD or CRRT) with and without supportive treatment, as well as different modalities of PD. Outcomes will include kidney function recovery, duration of renal replacement therapy, and laboratory index.[10] The review is scheduled to be completed in February 2017 (see Table 2).

Table 2. Key Question 2a. What are the associated benefits?: Evidence reviews.

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
Among hemofiltration and/or hemodialysis continuous renal replacement therapies (CRRTs)				
Friedrich et al., 2012[6]	Hemofiltration compared to hemodialysis for acute kidney injury: Systematic review and meta-analysis	CENTRAL, MEDLINE, EMBASE and grey literature from database inception to June 2012. The review included 10 parallel and 9 cross-over RCTs.	Conducted a meta-analysis to compare hemofiltration vs. hemodialysis (e.g., CVVH, CVVHD) on mortality, dialysis dependence, and other clinical outcomes. Study populations were ICU patients (one pediatric study).	From full text: There was no difference in mortality or other clinical outcomes. Dialysis dependence in survivors at follow up was not different between groups. From abstract: "Data from small RCTs do not suggest beneficial clinical outcomes from hemofiltration, but confidence intervals were wide. Hemofiltration may increase clearance of medium to larger molecules."
Among hemofiltration and/or hemodialysis - continuous versus extended daily or intermittent renal replacement therapies				
Zhang et al., 2015[9]	Extended daily dialysis versus continuous renal replacement therapy for acute kidney injury: a meta-analysis	CENTRAL, MEDLINE, EMBASE, a Chinese database (Sino-Med), Google Scholar, and major nephrology journals from database inception to August 2014. The review	Compared EDD to CRRT on mortality, kidney recovery, ICU days, and fluid removal.	From full text: For RCTs there was no difference in mortality rate between EDD and CRRT. However, EDD was associated with lower risk for mortality in observational studies. There was no significant

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
		included 7 RCTs and 10 observational studies.		difference in kidney recovery rate with EDD in comparison to CRRT in both RCTs and observational studies. Results of a meta-analysis found that EDD was associated with a higher fluid removal rate.
Schneider et al., 2013[8]	Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: A systematic review and meta-analysis	MEDLINE and EMBASE from database inception to July 2012. The review included 7 RCTs and 16 observational studies.	Compared IRRT to CRRT on dialysis dependence. All but one study involved ICU populations.	"Among AKI survivors, initial treatment with IRRT might be associated with higher rates of dialysis dependence than CRRT."
Among peritoneal dialysis (PD) modalities or compared to hemofiltration and/or hemodialysis				
Jiang et al., 2012[7] Cochrane	Tidal versus other forms of peritoneal dialysis for acute kidney injury	CENTRAL, MEDLINE, EMBASE and grey literature from database inception to February 2012. The review included 1 cross-over RCT.	Compared tidal PD (TPD) to continuous equilibrating PD (CEPD) on creatinine and blood urea nitrogen clearance, and other clinical outcomes.	"At present, there is *insufficient* RCT evidence to enable evaluation of the effect of TPD in patients with AKI." In addition, "these findings may not apply to the patient population in the developed countries due to differences in aetiologies, co-morbidities and level of hypercatabolism."
Chionh et al., 2013[5]	Use of peritoneal dialysis in AKI: A systematic review	CENTRAL, MEDLINE, and CINAHL from database inception to July 2012. The review included 4 RCTs, 8 prospective and 13 retrospective studies.	Compared all forms of PD to EBP, including IHD, DHD, CRRT (CVVH, CVVHDF) on mortality. ICU populations ranged from 13.3-100%.	"There is currently no evidence to suggest significant differences in mortality between peritoneal dialysis and extracorporeal blood purification in AKI."
Liu et al., 2015[10] Cochrane Protocol Anticipated completion February 2017	Peritoneal dialysis for acute kidney injury	CENTRAL, MEDLINE, EMBASE and grey literature from database inception.	Comparators will include PD (all modalities) with and without supportive treatment vs. HD (including all different modalities of IHD or CRRT) with and without supportive treatment, as well as different modalities of PD. Outcomes will include kidney function	N/A

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
			recovery, duration of dialysis, and laboratory index.	

*Summaries from full text are noted when applicable. Abbreviations: AKI=Acute Kidney Injury; CENTRAL=Cochrane Central Register of Controlled Trials; CEPD=Continuous Equilibrating Peritoneal Dialysis (; CRRT=Continuous Renal Replacement Therapy; CVVHDF=Continuous Veno-Venous Hemodiafiltration; CVVH=Continuous Veno-Venous Hemofiltration; DHD=Daily Hemodialysis; EBP= Extracorporeal Blood Purification; EDD=Extended Daily Dialysis; HD=Hemodialysis; ICU=Intensive Care Unit; IHD=Intermittent Hemodialysis; IRRT=Intermittent Renal Replacement Therapy; PD=Peritoneal Dialysis; RCT=Randomized Controlled Trial; TPD=Tidal Peritoneal Dialysis

Key question 2.b.i. What are the associated harms and costs among hemofiltration and/or hemodialysis continuous renal replacement therapies (CRRTs)?

A new evidence review would not be duplicative. We identified a 2012 meta-analysis, comparing hemofiltration to hemodialysis among ICU patients.[6] Findings indicate no difference in organ dysfunction and a shorter time to filter failure with hemofiltration. No other harms were examined.

Key question 2.b.ii. What are the associated harms and costs of continuous versus extended daily or intermittent hemofiltration and/or hemodialysis?

A new evidence review would not be duplicative. We identified one review comparing EDD to CRRT on episodes of vasopressure escalation and cost. Findings indicate no significant difference between EDD and CRRTs on episodes of vasopressure escalation, and that costs associated with EDD were lower (see Table 3).[9] No other harms were examined. We identified no reviews examining costs.

Key question 2.b.iii. What are the associated harms and costs among peritoneal dialysis (PD) modalities, or PD versus hemofiltration and/or hemodialysis

A new evidence review would be duplicative. We identified two reviews[5,7] (one Cochrane),[7] and one Cochrane protocol[10] examining peritoneal dialysis. A 2012 Cochrane review compared tidal PD to other forms of PD. The review included only one study, which compared tidal PD to continuous equilibrating PD (CEPD), and found that tidal PD consumed less time, and was less expensive than CEPD.[7] A second review compared PD to various forms of HD, and found the overall incidence of peritonitis to be 12.4% (see Table 3).[5]

The in-process Cochrane review will compare PD with and without supportive treatment with HD (including all different modalities of IHD or CRRT) with and without supportive treatment, as well as different modalities of PD. Outcomes will include cost, and adverse events such as bleeding, peritonitis, respiratory insufficiency, and hypoalbuminemia.[11] The review is scheduled to be completed in February 2017 (see Table 3).

Table 3. Key Question 2b. What are the associated hams and costs?: Evidence reviews

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
Among hemofiltration and/or hemodialysis continuous renal replacement therapies (CRRTs)				
Friedrich et al., 2012[6]	Hemofiltration compared to hemodialysis for acute kidney injury: Systematic review and meta-analysis	CENTRAL, MEDLINE, EMBASE and grey literature from database inception to June 2012. The review included 10 parallel and 9 cross-over RCTs.	Conducted a meta-analysis to compare hemofiltration vs. hemodialysis (e.g., CVVH, CVVHD) on filter life and organ dysfunction. Study populations were ICU patients (one pediatric study).	From full text: There was no difference on organ dysfunction and a shorter time to filter failure associated with hemofiltration.
Among hemofiltration and/or hemodialysis - continuous versus extended daily or intermittent renal replacement therapies				
Zhang et al., 2015[9]	Extended daily dialysis versus continuous renal replacement therapy for acute kidney injury: a meta-analysis	CENTRAL, MEDLINE, EMBASE, a Chinese database (Sino-Med), Google Scholar, and major nephrology journals from database inception to August 2014. The review included 7 RCTs and 10 observational studies.	Compared EDD to CRRT on episodes of vasopressure escalation and cost.	From full text: There was no significant difference between EDD and CRRTs on episodes of vasopressure escalation. All results indicated that costs were lower with EDD compared to CRRT.
Among peritoneal dialysis (PD) modalities or compared to hemofiltration and/or hemodialysis				
Jiang et al., 2012[7] Cochrane	Tidal versus other forms of peritoneal dialysis for acute kidney injury	CENTRAL, MEDLINE, EMBASE and grey literature from database inception to February 2012. The review included 1 cross-over RCT.	Compared TPD to continuous equilibrating PD (CEPD) on time and cost. No included studies included adverse events.	From full text: “Tidal PD consumed less time, and was less expensive than CEPD.”
Chionh et al., 2013[5]	Use of peritoneal dialysis in AKI: A systematic review	CENTRAL, MEDLINE, and CINAHL from database inception to July 2012. The review included 4 RCTs, 8 prospective and 13 retrospective studies.	Examined all forms of PD to EBP, including IHD, DHD, CRRT (CVVH, CVVHDF) on peritonitis. ICU populations ranged from 13.3-100%.	From full text: “Overall incidence of peritonitis was 12.4%, and it ranged from 0% to 40% in individual studies.”
Liu et al., 2015[11] Cochrane Protocol Anticipated completion February 2017	Peritoneal dialysis for acute kidney injury	CENTRAL, MEDLINE, EMBASE and grey literature from database inception.	Comparators will include PD (all modalities) with and without supportive treatment vs. HD (including all different modalities of IHD or CRRT) with and	N/A

			without supportive treatment, as well as different modalities of PD. Relevant outcomes will include cost, and adverse events such as bleeding, peritonitis, respiratory insufficiency, and hypoalbuminemia.	

*Summaries from full text are noted when applicable. Abbreviations: CENTRAL=Cochrane Central Register of Controlled Trials; CEPD=Continuous Equilibrating Peritoneal Dialysis; CRRT=Continuous Renal Replacement Therapy; CVVHDF=Continuous Veno-Venous Hemodialfiltration; CVVH=Continuous Veno-Venous Hemofiltration; DHD=Daily Hemodialysis; EBP=Extracorporeal Blood Purification; EDD=Extended Hemodialysis; HD=Hemodialysis; ICU=Intensive Care Unit; IHD=Intermittent Hemodialysis; PD=Peritoneal Dialysis; RCT=Randomized Controlled Trial; TPD=Tidal Peritoneal Dialysis

Key Question 3

For outcomes such as renal recovery, quality of life, and mortality for individuals with AKI-D, what is the effect of, (a) dose, (b) timing/initiation, and (c) fluid composition?

We identified six evidence reviews[10,12-16] examining the effect of dose, timing, or fluid composition on outcomes in critically ill patients with AKI-D (or acute renal failure [ARF] requiring dialysis).

Key question 3a. Dose.

A new evidence review would not be duplicative. We identified a 2011 evidence review comparing high to low intensity CRRT in critically ill patients. Findings indicate no difference in 28-day survival.[14] No other outcomes were examined (Table 4).

Table 4. Key Question 3a. For outcomes such as renal recovery, quality of life, and mortality for individuals with AKI-D, what is the effect of dose?: Evidence reviews

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
Negash et al., 2011[14]	Intensity of continuous renal replacement therapy in acute kidney injury in the intensive care unit: a systematic review and meta-analysis	CENTRAL, MEDLINE, EMBASE, ISI Web of Science from database inception to February 2010. The review included 5 RCTs.	Compared high-intensity vs low-intensity CRRT on 28-day survival.	"In critically ill patients with acute kidney injury, the high-dose CRRT did not reduce mortality at 28 days."

*Summaries from full text are noted when applicable. Abbreviations: CENTRAL= Cochrane Central Register of Controlled Trials; CRRT=Continuous Renal Replacement Therapy; RCT=Randomized Controlled Trial

Key question 3b. Timing/initiation.

A new evidence review would be duplicative. Three reviews compared early vs. late initiation of renal replacement therapy (RRT) on mortality,[10,13,16] All three reviews concluded that early initiation resulted in better outcomes (Table 5).[10,13,16]

Table 5. Key Question 3b. For outcomes such as renal recovery, quality of life, and mortality for individuals with AKI-D, what is the effect of timing/initiation?: Evidence reviews

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
Liu et al., 2014[10] Cochrane	Early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury after cardiac surgery: a systematic review and meta-analysis	CENTRAL, MEDLINE, EMBASE from database inception to January 2013. The review included 2 RCTs and 9 retrospective cohort studies.	Compared early vs. late initiation of RRT on 28-day mortality and ICU length of stay.	"Early initiation of RRT for patients with AKI after cardiac surgery revealed lower 28-days mortality and shorter ICU length of stay."
Wang and Jie Yuan, 2012[16]	Timing of initiation of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis	PubMed, ISI Web of Science and EMBASE from 1990 to August 2011. The review included 3 RCTs, 2 prospective and 10 retrospective comparative cohort studies.	Compared early vs. late initiation of RRT (CRRT and IHD) on mortality.	""Early" CRRT and "early" IHD both could reduce the mortality of patients with acute kidney injury compared with "late" CRRT or IHD."
Karvellas et al., 2011[13]	A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis	PUBMED, EMBASE, Scopus, Web of Science and CENTRAL to July 2010. Included 2 RCTs, four prospective cohort studies, and nine retrospective cohort studies	Compared early vs. late initiation of RRT (CRRT and IHD) on 28-day mortality.	"Earlier institution of RRT in critically ill patients with AKI may have a beneficial impact on survival. However, this conclusion is based on heterogeneous studies of variable quality and only two randomized trials. In the absence of new evidence from suitably-designed randomized trials, a definitive treatment recommendation cannot be made."

*Summaries from full text are noted when applicable. Abbreviations: AKI= Acute Kidney Injury; CENTRAL= Cochrane Central Register of Controlled Trials; CRRT=Continuous Renal Replacement Therapy; ICU=Intensive Care Unit; IHD=Intermittent Hemodialysis; RCT=Randomized Controlled Trial; RRT=Renal Replacement Therapy

Key question 3c. Fluid composition.

A new evidence review comparing bicarbonate vs. lactate-buffered fluids would be duplicative. We identified both a Cochrane[15] and another review[12] comparing bicarbonate to lactate-buffered solutions on outcomes such as serum creatinine, hypotensive episodes, and mortality. (Table 6). However, a new review examining anticoagulants would not be duplicative. We identified no existing or in-process reviews.

Table 6. Key Question 3c. For outcomes such as renal recovery, quality of life, and mortality for individuals with AKI-D, what is the effect of fluid composition?: Evidence reviews

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
Tian et al., 2015[15] Cochrane	Bicarbonate- versus lactate-buffered solutions for acute continuous haemodiafiltration or haemofiltration	CENTRAL, MEDLINE, EMBASE and grey literature from database inception to January 2015. The review included 1 parallel and 3 cross-over RCTs.	Compared bicarbonate-buffered vs lactate-buffered dialysate. Outcomes included mortality, serum bicarbonate levels, and serum creatinine, etc., and harms such as cardiovascular and hypotensive events.	Patients treated with bicarbonate-buffered solutions may experience fewer cardiovascular events, lower serum lactate levels, higher mean arterial pressure and less hypotensive events. There were no differences in mortality."
Bai et al., 2014[12]	Bicarbonate versus lactate solutions for acute peritoneal dialysis	CENTRAL, MEDLINE, EMBASE and grey literature from database inception to unspecified date. The review included 1 RCT.	Compared bicarbonate-buffered vs lactate-buffered dialysate on mortality and other clinical outcomes.	"There is no strong evidence that any clinical advantage for patients requiring acute PD for AKI when comparing conventional (lactate) with low glucose degradation products (GDP) dialysis solutions (bicarbonate)."

*Summaries from full text are noted when applicable. Abbreviations: AKI= Acute Kidney Injury; CENTRAL= Cochrane Central Register of Controlled Trials; CRRT=Continuous Renal Replacement Therapy; ICU=Intensive Care Unit; IHD=Intermittent Hemodialysis; GDP=Glucose Degradation Products; PD=Peritoneal Dialysis; RCT=Randomized Controlled Trial; RRT=Renal Replacement Therapy

Key question 3d. Session time/length.

We identified no evidence reviews examining the time or length of renal replacement therapy sessions.

Key Question 4

What are early and late predictors of renal function non-recovery and mortality in individuals with AKI-D?

We identified no evidence reviews examining early and late predictors of renal function non-recovery and mortality in individuals with AKI-D.

Key Question 5

For laboratory monitoring and clinical assessment of individuals with AKI-D:

Key question 5a. What are the optimal frequency and parameters to identify renal recovery and complications of AKI-D or associated treatments?

We identified no evidence reviews examining the optimal frequency or parameters of laboratory monitoring or clinical assessment of individuals with AKI-D.

Key question 5b. How do the frequency or parameters differ from individuals with ESRD?

We identified no evidence reviews examining differences in the optimal frequency or parameters of laboratory monitoring or clinical assessment of individuals with AKI-D as compared with individuals with ESRD.

Impact of New Evidence Review

The topic, Acute Kidney Injury and its associated key questions would have potential impact. Since 2012, CMS policy has prohibited reimbursement for AKI-D treatment at ESRD facilities.[4] However, in 2015, Congress amended the Social Security Act to permit reimbursement for AKI-D treatment at ESRD facilities beginning in Jan 2017. Current standards of care for patients with AKI-D requiring outpatient renal replacement therapy are unclear. While there is little direct evidence related to the treatment of individuals with AKI-D in outpatient settings, a new systematic review examining the relevant existing indirect evidence on individuals AKI-D in ICU settings will help to inform CMS policies and standards of care for this patient population in outpatient settings.

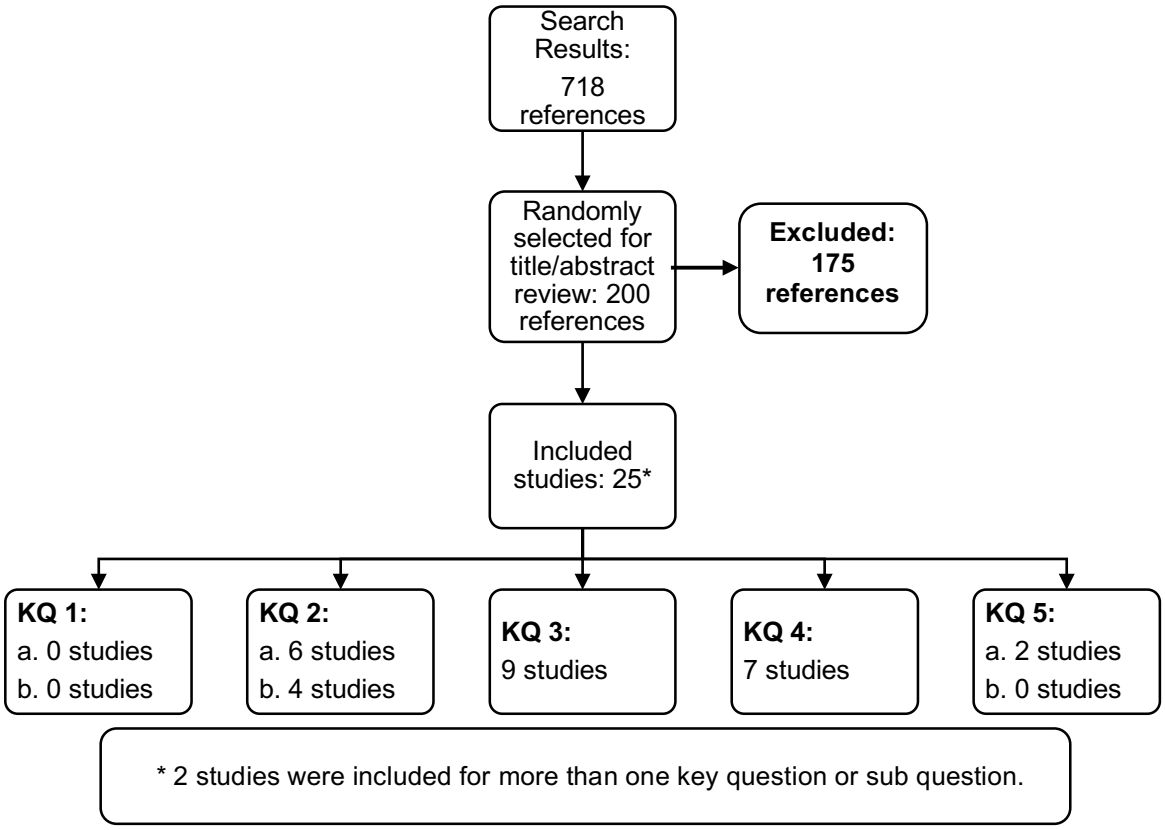
Primary Research

Literature Search.

The literature search identified 718 unique titles (see Appendix C for links to the search results). We randomly selected 200 titles and abstracts to review to evaluate the feasibility of conducting a new evidence review. Upon abstract review, we identified 26 studies relevant to one or more of the key questions in the nomination. One identified study was a Cochrane systematic review published in 2007.[17] In order to capture the most recent evidence, we included only systematic reviews published from 2011 to the present; thus, excluded this review, for a total of 25 studies. Based on an inclusion percentage of 12.5%, our expected total number of studies across key questions is 90 (see Appendix C for more detail).

Figure 2 shows the citation yield from electronic database searches, numbers of exclusions, and the final yield of included studies delineated by key question.

Figure 2. Literature Search Results



Key Question 1

For individuals with a diagnosis of Acute Kidney Injury requiring dialysis (AKI-D), are certain treatment strategies for the clinical features of AKI (e.g., fluid volume, blood pressure, anemia, nutrition, and bone mineral disease) more likely to result in improved outcomes?

Key question 1a. What are the associated benefits, such as renal recovery, quality of life, and mortality?

We identified no studies related to the benefits of treatment strategies for the clinical features of AKI-D.

Key question 1b. What are the associated harms and costs?

We identified no studies related to the harms or costs of treatment strategies for the clinical features of AKI-D.

Key Question 2

What are the optimal renal replacement modalities (including frequency) for outcomes such as renal recovery, quality of life, and mortality?

Key question 2a. What are the associated benefits?

From the 200 randomly selected studies we reviewed, we identified six studies[18-23] (three RCTs,[20-22] one prospective,[23] and two retrospective cohort studies)[18,19] examining the benefits of different renal replacement therapy modalities, for an expected total of 22 relevant studies (see Table 7 and Appendix D for more detail).

Key question 2.a.i. What are the associated benefits among hemofiltration and/or hemodialysis continuous renal replacement therapies (CRRTs)?

We identified one retrospective cohort study comparing continuous veno-venous hemofiltration (CVVH) versus continuous veno-venous hemodiafiltration (CVVHDF) in critically ill patients. Results indicated no difference on mortality or hospital length of stay.[18]

Key question 2.a.ii. What are the associated benefits associated with continuous versus extended daily or intermittent hemofiltration and/or hemodialysis?

We identified three studies[19,21,23] (one RCT,[21] one prospective,[23] and one retrospective cohort study)[19] comparing continuous to intermittent hemodialysis in ICU patients. Two studies examined the use of CVVH, one compared to IHD,[21] and the other compared to sustained low-efficiency dialysis (SLED).[23] The other study compared (undefined) CRRT to IHD.[19] Outcomes included renal recovery,[19,21] hospital length of stay,[21,23] and mortality.[19,23]

Key question 2.a.iii. What are the associated benefits among peritoneal dialysis (PD) modalities, or PD versus hemofiltration and/or hemodialysis?

Two studies compared variants of PD and HD, both examining HVPD – one compared to EDD, and the other to DHD. Outcomes included metabolic control,[20] renal recovery,[20,22] mortality,[20,22] and mean ICU or hospital stay.[22]

Table 7. Key Question 2a. What are the associated benefits?: Literature search

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
Among hemofiltration and/or hemodialysis continuous renal replacement therapies (CRRTs)				
AlEnezi et al., 2014[18]	Continuous veno-venous hemofiltration versus continuous veno-venous hemodiafiltration in critically ill patients: A retrospective cohort study from a Canadian tertiary centre	153 ICU patients Compared CVVH (n = 94) to CVVHDF (n = 59).	Hospital and 30-day mortality were similar in the CVVH and CVVHDF groups (OR 0.85 [95% CI 0.38 to 1.89]; P=0.69 and OR 1.35 [95% CI 0.62 to 2.95]; P=0.45, respectively). There was no difference in hospital length of stay (mean difference -34.14 [95% CI -72.92 to 4.65]; P=0.08).	"The present retrospective review suggests that the use of CVVH does not reduce mortality or hospital length of stay when compared with CVVHDF."
Among hemofiltration and/or hemodialysis - continuous versus extended daily or intermittent renal replacement therapies				
Lins et al., 2009[21]	Intermittent versus continuous renal	316 ICU patients Compared IHD (n	No difference between IHD and CVVH could be observed in the duration of	"Modality of RRT, either CRRT or IRRT, had no impact on the outcome in

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
	replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial	= 144) to CVVH (n = 172)	ICU stay or hospital stay. In survivors, renal recovery at hospital discharge was comparable between both groups.	ICU patients with AKI."
Wu et al., 2010[23]	Sustained low-efficiency dialysis versus continuous veno-venous hemofiltration for postsurgical acute renal failure	101 surgical ICU patients Compared CVVH (n=63) to SLED (n=38)	On an intention-to-treat basis, the ICU and 30-day AHD mortality rates were significantly higher in the CVVH group (*P* = .003 and .020, respectively	"Among the postsurgical patients requiring acute dialysis with severe fluid overload or moderately unstable hemodynamics, the patients treated with SLED had a higher first postdialysis MAP than those treated with CVVH, which led to lower mortality."
Bell et al., 2007[19]	Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure	2202 ICU patients Compared IHD (n = 158) to CRRT (944)	8.3% of CRRT patients (confidence interval, CI, 6.6-10.2) never recovered renal function compared to 16.5% (CI 11.0-23.2) of IHD patients.	"The use of CRRT is associated with better renal recovery than IHD, but mortality does not differ between the groups."
Among peritoneal dialysis (PD) modalities or compared to hemofiltration and/or hemodialysis				
Ponce et al., 2013[22]	A randomized clinical trial of high volume peritoneal dialysis versus extended daily hemodialysis for acute kidney injury patients.	143 ICU patients Compared EDD (n = 82) to HVPD (n = 61)	There was no difference between the two groups in relation to median ICU stay, recovery of kidney function, need for chronic dialysis, and hospital mortality. The groups were different in metabolic and fluid control. After adjustments were made, the odds of death associated with HVPD was 1.4 (95 % CI 0.7-2.4, p = 0.19).	"Despite faster metabolic control and higher dialysis dose and ultrafiltration with EDD, this study provides no evidence of a survival benefit of EDD compared with HVPD. The limitations of this study were that the results were not presented according to the intention to treat and it did not control other supportive management strategies as nutrition support and timing of dialysis initiation that might influence outcomes in AKI."
Gabriel et al., 2008[20]	High volume peritoneal dialysis vs daily	120 patients with ATN in a tertiary care hospital	Metabolic control, mortality (58 and 53%), and renal recovery (28 and 26%) were	"HVPD and DHD can be considered as alternative forms of RRT in AKI."

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
	hemodialysis: a randomized, controlled trial in patients with acute kidney injury	Compared HVPD (n=60) to daily HD (DHD; n=60)	similar in both groups, whereas HVPD was associated with a significantly shorter time to renal recovery.	

*Summaries from full text are noted when applicable. Abbreviations: AHD=After Hospital Discharge; AKI=Acute Kidney Injury; ARF=Acute Renal Failure; CRRT= Continuous Renal Replacement Therapy; CVVH=Continuous Veno-Venous Hemofiltration; CVVHDF=Continuous Veno-Venous Hemodiafiltration; DHD=Daily Hemodialysis; EDD= Extended Daily Dialysis; HD=Hemodialysis; HVPD=High Volume Peritoneal Dialysis; ICU=Intensive Care Unit; IHD=Intermittent Hemodialysis; IRRT=Intermittent Renal Replacement Therapy; MAP=Main Arterial Pressure; RRT=Renal Replacement Therapy; SLED=Sustained Low-Efficiency Dialysis

Key question 2b. What are the associated harms and costs?

From the 200 randomly selected studies we examined, we identified four studies[23-26] examining harms or costs associated with different modalities for renal replacement therapy (one RCT,[26] two retrospective cohort,[23,24] and one Markov modeling study)[25] for an expected total of 14 relevant studies (see Appendix D for more detail).

Key question 2.b.i. What are the associated harms and costs among hemofiltration and/or hemodialysis continuous renal replacement therapies (CRRTs)?

We identified no studies comparing the harms or costs associated with CRRT modalities

Key question 2.b.ii. What are the associated harms or costs associated with continuous versus extended daily or intermittent hemofiltration and/or hemodialysis?

All four identified studies compared continuous to intermittent hemodialysis in critically ill patients. Related to harms, two studies examined the use of CVVH, one compared to SLED,[23] and the other compared to SLED and IHD.[26] The other compared CRRT ("generally CVVHDF") to SLED and IHD.[24] Examined harms included bleeding complications,[26] hemodynamic instability,[24] and severe hypotension.[23]

One study compared the cost effectiveness of CRRT and IHD. Findings indicated that CRRT was associated with higher costs (see Table 8).[25]

Key question 2.b.iii. What are the associated harms or costs among peritoneal dialysis (PD) modalities, or PD versus hemofiltration and/or hemodialysis?

We identified no studies comparing the harms and costs associated among PD modalities or PD compared to HD.

Table 8. Key Question 2b. What are the associated harms and costs?: Literature search

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
Among hemofiltration and/or hemodialysis - continuous versus extended daily or intermittent renal replacement therapies				
Pschowski et al., 2015[26]	Effects of dialysis modality on blood loss, bleeding complications and transfusion requirements in critically ill patients with dialysis-dependent acute renal failure	252 patients with ARF Compared CVVH(n=30), SLED (n=13), and IHD (n=34)	Major all-cause bleeding complications were observed in 23% IHD vs 26% of CVVH group patients (P=0.95). Under CVVH, the rate of RRT-related blood loss events (57.4% vs 30.4%, P=0.01) and mean total blood volume lost was increased (222.3+/-291.9 vs 112.5+/-222.7 ml per patient, P <0.001). Transfusion rates did not differ between the study groups.	"Procedural and non-procedural blood loss may often be observed in critically ill patients on RRT. In CVVH-treated patients, procedural blood loss was increased but overall transfusion rates remained unchanged. Our data show that IHD and CVVH may be regarded as equivalent approaches in critically ill patients with dialysis-dependent acute renal failure in this regard."
Fieghen et al., 2010[24]	The hemodynamic tolerability and feasibility of sustained low efficiency dialysis in the management of critically ill patients with acute kidney injury	77 critically ill patients CRRT (generally CVVHDF; n=30), SLED (n=13), IHD (n=34)	Hemodynamic instability occurred during 22 (56.4%) SLED and 43 (50.0%) CRRT sessions (p = 0.51). Session interruption occurred in 16 (16.3), 30 (34.9) and 11 (28.2) of IHD, CRRT and SLED therapies, respectively.	In critically ill patients with AKI, the administration of SLED is feasible and provides comparable hemodynamic control to CRRT.
Wu et al., 2010[23]	Sustained low-efficiency dialysis versus continuous veno-venous hemofiltration for postsurgical acute renal failure	101 surgical ICU patients Compared CVVH (n=63) to SLED (n=38)	Four patients (10.5%) in the SLED group were shifted to CVVH because of severe hypotension at days 6, 18, 27, and 30, and they all died.	"Among the postsurgical patients requiring acute dialysis with severe fluid overload or moderately unstable hemodynamics, the patients treated with SLED had a higher first postdialysis MAP than those treated with CVVH, which led to lower mortality."
Klarenbach et al., 2009[25]	Economic evaluation of continuous renal replacement	Critical care patients (n=not specified)	CRRT was associated with similar health outcomes but higher costs. In scenarios considering alternate cost	Given the higher costs of providing CRRT and absence of demonstrated benefit, IHD is the preferred

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
	therapy in acute renal failure	Compared IHD to CRRT	sources, and higher intensity of IHD (including daily and longer duration IHD), CRRT remained more costly.	modality in critically ill patients who are candidates for either IHD or CRRT

*Summaries from full text are noted when applicable. Abbreviations: AKI=Acute Kidney Injury; ARF=Acute Renal Failure; CRRT=Continuous Renal Replacement Therapy; CVVH=Continuous Veno-Venous Hemofiltration; CVVHDF=Continuous Veno-venous Hemodiafiltration; ICU=Intensive Care Unit; IHD= Intermittent Hemodialysis; MAP=Main Arterial Pressure; RRT=Renal Replacement Therapy; SLED=Sustained Low-Efficiency Dialysis

Key Question 3

For outcomes such as renal recovery, quality of life, and mortality for individuals with AKI-D, what is the effect of, (a) dose, (b) timing/initiation, and (c) fluid composition?

Of the 200 randomly selected studies we examined, nine (four RCTs,[27-30] one prospective cohort,[31] and four retrospective cohort)[32-35] studies examined the effect of the timing, length, dose, intensity, fluid composition, or anticoagulants, for an expected total of 32 relevant studies (see Appendix D for more detail).

Key question 3a. Dose.

We identified two RCTs[29,30] and one retrospective cohort study[34] examining dose. One RCT compared CVVHDF to CVVH to determine if increasing the dialysis dose by adding a dialysis flow rate to CVVH improved survival.[30] Two studies compared higher to lower intensity/volume dialysis[29,34] on renal recovery, mortality, and cost (Table 9).[34]

Table 9. Key Question 3a. For outcomes such as renal recovery, quality of life, and mortality for individuals with AKI-D, what is the effect of dose?: Literature search

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
Randomized Controlled Trials				
Saudan et al., 2006[30]	Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure	206 ICU patients with ARF Compared CVVHDF + dialysate (n = 104) to CVVH (n = 102) to determine if increasing the dialysis dose by adding a dialysis flow rate to CVVH	Twenty-eight-day and three months survivals was increased in the CVVHDF group (59% vs 39% (P=0.03); 59% vs 34% (P=0.0005). Renal recovery rate among survivors was not affected by the type of renal replacement therapy.	"These results suggest that increasing the dialysis dose especially for low molecular weight solutes confers a better survival in severely ill patients with ARF."

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
		improved outcomes.		
Ponce et al., 2011[29]	Different prescribed doses of high-volume peritoneal dialysis and outcome of patients with acute kidney injury	61 critically ill patients Compared higher- (n=30) to lower-intensity (n=31) PD	At 30 days after randomization, mortality was similar in the two groups (55% higher vs 53% lower, p = 0.83). However, the prescribed dose in the higher-intensity group was significantly different from the actual dose (0.8 Kt/V vs. 0.59 Kt/V, p = 0.04).	"In critically ill patients with AKI, an intensive PD dose did not lower the mortality or improve the recovery of kidney function or metabolic control."
Retrospective Cohort				
Paterson et al., 2014[34]	Clinical and economic impact of a switch from high- to low-volume renal replacement therapy in patients with acute kidney injury	366 ICU patients Compared high volume RRT (n=187) to low volume RRT (n=179)	There was no difference in in-hospital mortality (77/187 (41%) vs 75/179 (42%), respectively, p = 0.92), ICU mortality (55/187 (29%) vs 61/179 (34%), respectively, p = 0.40), duration of organ support or extent of renal recovery between the high- and low-volume cohorts.	"In conclusion, a switch from high- to low-volume continuous haemodiafiltration had minimal effects on clinical outcomes and resulted in marked cost savings."

*Summaries from full text are noted when applicable. Abbreviations: AKI=Acute Kidney Injury; ARF=Acute Renal Failure; CVVH= Continuous Veno-Venous Hemofiltration; CVVHDF= Continuous Veno-Venous Hemodiafiltration; ICU=Intensive Care Unit; RRT=Renal Replacement Therapy.

Key question 3b. Timing/initiation.

We identified one retrospective cohort study examining the timing of renal replacement therapy initiation and the number of sessions to recovery by group[32] on mortality (Table 10).

Table 10. Key Question 3b. For outcomes such as renal recovery, quality of life, and mortality for individuals with AKI-D, what is the effect of timing/initiation?: Literature search

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
Retrospective Cohort				
Manche et al., 2008[32]	Early dialysis in acute kidney injury after cardiac surgery	71 patients who developed AKI-D after cardiac surgery Examined the timing of dialysis,	13 of the 15 patients who received dialysis later died peri-operatively (87%). 14 out of 56 patients who received dialysis earlier died after receiving dialysis (25%). The two surviving	Earlier dialysis resulted in significantly improved survival (P=0.00001).

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
		comparing later IHD (as a last resort when it became impossible to correct hyperkalaemia; n = 15) to earlier IHD (immediately when oliguria occurred and did not respond to fluid replacement and single dose intravenous diuretics; n = 56). Also compared the number of dialysis sessions before recovery by group.	patients in the later group received six and seven sessions before recover. The 42 early dialysis survivors required a mean of 1.8±0.9 dialysis sessions before recovery.	

*Summaries from full text are noted when applicable. Abbreviations: AKI-D=Acute Kidney Injury requiring Dialysis; IHD; Intermittent Hemodialysis.

Key question 3c. Fluid composition.

We identified one RCT,[28] one prospective cohort study,[31] and one retrospective cohort study[33] comparing anticoagulants (i.e., regional citrate,[28] unfractionated heparin [UFH],[28,31,33] dermatan sulfate [DS])[31] on bleeding[28,31,33] and mortality, [28,31,33] and one retrospective cohort study examining the use of intravenous sodium phosphate supplementation (PS) on hypophosphatemia, oliguria during IHD, duration of AKI, and renal recovery[35](Table 11).

Table 11. Key Question 3c. For outcomes such as renal recovery, quality of life, and mortality for individuals with AKI-D, what is the effect of fluid composition?: Literature search

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
Randomized Controlled Trials				
Hetzel et al., 2011[28]	Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous veno-venous	174 mechanically ventilated patients Compared CVVH using	Comparison of standard bicarbonate from Day 3 to Day 11 revealed no difference between both treatment modalities. Use of citrate resulted in less systemic anticoagulation,	"Citrate may be used as a regional anticoagulant and the only buffering agent in CVVH with adequate treatment efficacy and safety. However, neither citrate

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
	haemofiltration: a prospective randomized multicentre trial	regional citrate anticoagulation (n= 87) vs. systemic anticoagulation with unfractionated heparin (n = 87)	a lower risk of bleeding and a longer haemofilter patency. Mortality was not influenced by the mode of anticoagulation.	nor heparin anticoagulation should be regarded as a therapeutic standard, since there is no advantage of one of these substances with regard to patient mortality."
		Prospective Cohort		
Vitale et al, 2008[31]	Effects of dermatan sulfate for anticoagulation in continuous renal replacement therapy	147 ICU patients with ARF receiving CRRT after cardiovascular surgery Compared CRRT anticoagulation using unfractionated heparin (UFH) (n=100, retrospective) to dermatan sulfate (DS) (n=47)	Median filter lifetime was 58 hours in DS-CRRT vs. 47 hours in UFH-CRRT ($p<0.001$). During CRRT, DS produced a smaller activated partial thromboplastin time increase ($p<0.01$). No significant differences were seen in basal hematology and hemostasis tests, platelet count, bleeding episodes or mortality.	"DS can be suggested as an anticoagulant for CRRT in patients who develop acute renal failure following major cardiovascular surgery."
		Retrospective Cohort		
Nagarik et al., 2010[33]	Comparative study of anticoagulation versus saline flushes in continuous renal replacement therapy	65 critically ill patients receiving CRRT Compared anticoagulant (unfractionated heparin; n=35) to saline flushes (n=30)	Patients receiving heparin had 16 bleeding episodes (0.45/patient) while only four bleeding episodes occurred in saline flush group (0.13/patient, $P < 0.05$). Mortality was 71% in heparin group and 67% in heparin free group.	"Frequent saline flushes is an effective mode of maintenance of extracorporeal circuit in CRRT when activated partial thromboplastin time is already on the higher side, with significantly decreased bleeding episodes."

*Summaries from full text are noted when applicable. Abbreviations: CRRT=Continuous Renal Replacement Therapy; CVVH= Continuous Veno-Venous Hemofiltration; DS=Dermatan Sulfate; DS-CRRT= Dermatan Sulfate Continuous Veno-Venous Hemofiltration; ICU=Intensive Care Unit; UFH=Unfractionated Heparin; UFH-CRRT=Unfractionated Heparin-Continuous Renal Replacement Therapy

Key question 3d. Session time/length.

We identified one RCT comparing six to ten hour extended daily dialysis sessions[27] on metabolic control, fluid balance, and hypotension (Table 12).

Table 12. Key Question 3. For outcomes such as renal recovery, quality of life, and mortality for individuals with AKI-D, what is the effect of time/length?: Literature search

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
Randomized Controlled Trials				
Albino et al., 2014[27]	Dialysis complications in AKI patients treated with extended daily dialysis: is the duration of therapy important?	75 ICU patients Examined the duration of EDD. Compared 6 hour EDD (n = 38) to 10 hour EDD (n = 37)	The 10-hour group showed higher refractory to clinical measures for hypotension and dialysis sessions were interrupted more often. Metabolic control and fluid balance were similar between groups.	Intradialysis hypotension was common in AKI patients treated with EDD. There was no difference in the prevalence of dialysis complications in patients undergoing different durations of EDD.

*Summaries from full text are noted when applicable. Abbreviations: AKI=Acute Kidney Injury; EDD=Extended Daily Dialysis; ICU=Intensive Care Unit

Key Question 4

What are early and late predictors of renal function non-recovery and mortality in patients with AKI-D?

From the 200 randomly selected studies we examined, we identified seven[23,30,36-40] (one RCT,[30] four prospective cohort,[23,38-40] and two retrospective cohort)[36,37] studies examining predictors of renal function outcomes, for an expected total of 25 relevant studies (see Appendix D for more detail).

Predictors examined included function recovery was associated with creatinine upon admission[38], acute renal failure,[38] APACHE II score,[30] age,[23,30,39] baseline blood urea nitrogen,[30] hemodiafiltration,[30] length of hospitalization,[40] cancer,[23] history of hypertension,[23,39] sepsis,[39] urine output,[39] serum creatinine and albumin levels,[37] acidosis and acidemia,[36] and recovery status at discharge.[37]

See Table 13 for more details.

Table 13. Key Question 4. What are early and late predictors that renal function will not recover in patients with AKI-D?: Literature search

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
Randomized Controlled Trials				
Saudan et al., 2006[30]	Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure	206 ICU patients with ARF CVVH (1-2.5 l/h replacement fluid) or continuous CVVHDF (1-2.5	Apache II score, age, baseline blood urea nitrogen, and hemodiafiltration (hazard ratio 0.59, 95% confidence interval 0.40-0.87; P=0.008) were independent predictors of survival at 90 days.	Apache II score, age, baseline blood urea nitrogen, and were independent predictors of survival at 90 days. When baseline blood urea nitrogen was replaced by baseline serum creatinine in the model,

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
		l/h replacement fluid+1-1.5 l/h dialysate)		hemodiafiltration remained a significant predictive factor
Prospective Cohort				
Ponce et al., 2012[39]	High-volume peritoneal dialysis in acute kidney injury: indications and limitations	150 patients High volume PD (HVPD)	Age and sepsis were identified as risk factors for death. In urine output, increase of 1 g in nitrogen balance and increase of 500 ml in ultrafiltration after three sessions were identified as protective factors.	"Age, sepsis, and urine output as well as nitrogen balance and ultrafiltration after three HVPD sessions were associated significantly with death."
Navas et al., 2012[38]	Renal replacement therapy in the critical patient: treatment variation over time	304 ICU patients RRT	The risk factors associated to mortality were creatinine upon admission (odds ratio [OR] 0.77; 95% confidence interval [95%CI] 0.61-0.97) and treatment with IHD alone (OR 0.37, 95%CI 0.16-0.87). The factors related to the recovery of renal function were creatinine upon admission (OR 1.98, 95%CI 1.12-3.48), acute renal failure (OR 0.11, 95%CI 0.04-0.34) and treatment with continuous techniques (OR 0.18, 95%CI 0.03-0.85).	On analyzing the mortality predictors in our study population, one of the variables correlated to increased mortality was creatinine upon admission---with higher values among the survivors. Since most of the patients were septic cases, we probably could deduce that since these subjects had higher creatinine levels, they were placed on dialysis earlier (though in our work, and as a limiting element of the study, the RRT starting time was not documented).
Wilson et al., 2012[40]	Creatinine generation is reduced in patients requiring continuous veno-venous hemodialysis and independently predicts mortality	103 patients in tertiary care CVVHD	Lower creatinine generation rate (CGR) was independently associated with in-hospital mortality in unadjusted analysis and after multivariable adjustment for measures of severity of illness.	Grading systems for severity of AKI fail to account for variation in CGR, limiting their ability to predict relevant outcomes. Calculation of CGR is superior to other risk metrics in predicting hospital mortality in this population.
Wu et al., 2010[23]	Sustained low-efficiency dialysis versus continuous veno-venous hemofiltration	101 ARF patients CVVH (n=63) or SLED (n=38)	Independent risk factors for 30-day AHD mortality included older age lower first postdialysis mean arterial pressure (MAP) (P = .021). A further linear	"Among the postsurgical patients requiring acute dialysis with severe fluid overload or moderately unstable hemodynamics, the patients treated with

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
	for postsurgical acute renal failure		regression analysis found that dialysis using SLED was associated with higher first postdialysis MAP (P = .003).	SLED had a higher first postdialysis MAP than those treated with CVVH, which led to lower mortality."
Retrospective Cohort				
Demirjian et al., 2008[36]	Alkalemia during continuous renal replacement therapy and mortality in critically ill patients	405 patients Bicarbonate based CRRT	Study subjects had on average 1.5 +/- 2.9 days where pH was greater than 7.45, and .4 days where serum bicarbonate level was greater than 28 mmol/L during a median of 9 days of CRRT. Increasing proportion of days with elevated pH or serum bicarbonate was not associated with increased mortality in multivariable analysis.	Alkalemia and alkalosis occur frequently during CRRT, but they are not associated with increased mortality. Persistent acidosis and acidemia while on CRRT was a strong predictor of poor outcome.
Duran and Concepcion, 2014[37]	Survival after acute kidney injury requiring dialysis: long-term follow up.	All AKI-D patients from 2000-2011 HD and CVVHD	Of the nonsurvivors, the only significant difference was a lower albumin at baseline (2.9 vs. 3.1 g/dL) (P < 0.05) and lower peak creatinine (5.5 vs. 6.8 mg/dL) (P < 0.05). The survival of the patients who recovered from kidney function at discharge was longer than the ones who did not recover (59.7 vs. 16 m, P < 0.05).	Factors affecting the survival included peak creatinine and status of recovery of kidney function at discharge.

*Summaries from full text are noted when applicable. Abbreviations: AHD=After Hospital Discharge; AKI=Acute Kidney Injury; AKI-D=Acute Kidney Injury-Dialysis; ARF=Acute Renal Failure; CGR=Creatinine Generation Rate; CRRT=Continuous Renal Replacement Therapy; CVVH=Continuous Veno-Venous Hemofiltration; CVVHDF=Continuous Veno-Venous Hemodiafiltration; HD=Hemodialysis; HVPD=High Volume Peritoneal Dialysis; ICU=Intensive Care Unit; IHD=Intermittent Hemodialysis; MAP=Main Arterial Pressure; PD=Peritoneal Dialysis; RRT=Renal Replacement Therapy; SLED=Sustained Low-Efficiency Dialysis

Key Question 5

For laboratory monitoring and clinical assessment of patients with AKI-D:

Key question 5a. What are the optimal frequency and parameters mitigate renal non-recovery and complications of AKI-D or associated treatments?

From the 200 randomly selected studies we examined, we identified two studies[41,42] examining the optimal frequency and/or parameters to identify renal recovery and complications of AKI-D

or associated treatments (one RCT[42] and one prospective cohort),[41] for an expected total of seven relevant studies (see Appendix D for more detail).

The prospective[41] cohort study examined online blood volume and temperature monitoring during IHD, as compared to historical controls on intradialytic hypotension. The RCT,[42] was a three-arm follow up study, comparing controls (IHD) to online blood volume monitoring to online blood volume and body temperature monitoring on hypotension. Results indicated no difference between groups.

See Table 14 for more details.

Table 14. Key Question 5a. For laboratory monitoring and clinical assessment of patients with AKI-D, what are the optimal frequency and parameters to identify renal recovery and complications of AKI-D or associated treatments?: Literature search

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
Randomized Controlled Trials				
du Cheyron et al., 2013[42]	Use of online blood volume and blood temperature monitoring during haemodialysis in critically ill patients with acute kidney injury: a single-centre randomized controlled trial	74 critically ill patients Online simultaneous blood volume monitoring (n = 59) vs online blood volume and blood temperature control (n = 56) vs. controls (standard IHD; n = 54).	Hypotension occurred in 16.6% treatments, with similar rates among the arms. Haemodynamic parameters and dialysis-related complications did not differ between therapies.	These results suggest that both actively controlled body temperature and UF profiled by online monitoring systems have no significant impact on the incidence of intradialytic hypotension in the ICU setting.
Prospective Cohort				
du Cheyron et al., 2010[41]	Blood Volume- and Blood Temperature -Controlled Hemodialysis in Critically Ill Patients: A 6-Month, Case-Matched, Open-Label Study	62 critically ill patients Online Blood volume and temperature monitoring during IHD (n=20) was compared to historical controls (standard IHD; n=42)	After adjustment for covariates, online monitoring of blood volume and blood temperature was significantly associated with a reduction in the intradialytic hypotension rate compared with the conventional protocol.	The combination of active controlled body temperature and profiled ultrafiltration by online monitoring systems is feasible and safe in critically ill AKI patients, and suggests possibilities for improvement in intradialytic hemodynamic stability.

*Summaries from full text are noted when applicable. Abbreviations: AKI=Acute Kidney Injury; ICU=Intensive Care Unit; IHD=Intermittent Hemodialysis; UF=Ultrafiltration

Key question 5b. How do the frequency or parameters for individuals with AKI-D differ from those with ESRD?

We identified no studies related to laboratory monitoring and clinical assessment differences in individuals with AKI-D as compared to those with ESRD.

Clinical Trials

We identified three open studies relevant to the key questions in the nomination. An RCT of children will compare carnitine to control for cardiac function.[43] Two studies will compare modalities for renal replacement therapy.[44,45] One study of children will collect information about the timing and dose of dialysis, as well as for urea, blood pressure, creatinine, proteinuria/creatinuria, renal disease, and acute graft to examine whether these factors relate to or predict renal recovery and other outcomes (see Table 15).[44]

Table 15. Potentially relevant clinical trials

Reference	Status	Summary	Related Key Question
Randomized Controlled Trials			
Moudgil et al. 2015[43]	Recruiting participants	Comparing daily carnitine to no carnitine on cardiac function and prevalence of carnitine deficiency in children with kidney failure on continuous dialysis (CRRT).	KQ1
University Hospital Inselspital, 2015[45]	Not yet open for patient recruitment	Continuous renal replacement therapy will be compared to intermittent renal replacement therapy on microbubble / cerebral microemboli in critically ill patients with dialysis-dependent acute kidney injury.	KQ2
Prospective Cohort			
Rennes University Hospital, 2015[44]	Recruiting participants	Children with acute kidney injury requiring dialysis will be observed for modalities of extra renal replacement therapy, including intermittent hemodialysis, continuous renal replacement therapies, and	KQ2, KQ3, KQ4

		peritoneal dialysis, as well as the dose, and timing of dialysis. Secondary outcomes will be current incidence, etiologies, and risk factors of modality and non-recovery of renal function (including urea, blood pressure, creatinine, report proteinuria / creatinuria, renal disease, acute graft).	

Abbreviations: AKI-D=Acute Kidney Injury-Dialysis; CRRT=Continuous Renal Replacement Therapy; IRRT=Intermittent Renal Replacement Therapy; PD=Peritoneal Dialysis; RCT=Randomized Controlled Trial

Value

A new systematic review examining the treatment of patients with AKI-D has potential value. While we identified no studies examining individuals with AKI-D in outpatient settings, the findings of a systematic review examining inpatients with AKI-D will impact clinical decision-making on how to best treat AKI-D to facilitate renal recovery, and will help to inform CMS policies for outpatient AKI-D treatments.

Summary of Findings and Conclusion

A new evidence review examining interventions for individuals with AKI-D is both appropriate and important. Approximately 10-30% of patients that survive in-hospital AKI-D require renal replacement therapy post-discharge.[4] However, there are currently no established guidelines for the treatment of AKI-D in outpatient settings.[46] The uncertainty around care for individuals with AKI-D in outpatient settings, combined with the upcoming change in CMS reimbursement policies result in the potential for a new AHRQ evidence review to make a significant impact.

There is little direct evidence related to the treatment of individuals with AKI-D in outpatient settings, as the bulk of the existing research examines patients in intensive or critical care units. However, a new AHRQ systematic review does have value. Until there is established research examining individuals with AKI-D in outpatient settings, a synthesis of the relevant indirect evidence has the potential to impact clinical decision-making and inform policy.

The nominator is aware of the paucity of research examining AKI-D in outpatient settings, as well as the potential for limited applicability to the population of interest. However, given the need to determine best practices and establish policies, the nominator is interested in a systematic review of the existing relevant indirect literature.

There are a number of existing and in-process systematic reviews examining the benefits and harms associated with different renal replacement modalities, as well as variables related to dose, timing/initiation of renal replacement therapy, and fluid composition. However, a new evidence review covering both the scope needed by the nominator to inform CMS policies, and

focused on the populations and outcomes most applicable to individuals with AKI-D in outpatient settings in the United States would not be duplicative. Original research related to some of the key questions of interest may be limited; however, a new evidence review will serve not only to guide clinical decision-making and policy, but particularly relevant for this patient population, identify research gaps and drive future research.

- Key Question 1a. Benefits of treatment strategies for the clinical features of AKI
  - A new evidence review *would not be duplicative*. We identified no completed or in-process evidence reviews examining benefits for the clinical features of AKI.
  - From the 200 randomly selected studies we examined, we identified no studies covering the scope of the key question.
- Key Question 1b. Harms and costs of treatment strategies for the clinical features of AKI
  - A new evidence review *would not be duplicative*. We identified no completed or in-process evidence reviews covering the scope of the key question.
  - From the 200 randomly selected studies we examined, we identified no studies examining benefits for the clinical features of AKI.
- Key Question 2a. Benefits of Renal Replacement Modalities
  - 2.a.i. Among hemofiltration and/or hemodialysis continuous renal replacement therapies
    - A new evidence *would be duplicative*. We identified a 2012 meta-analysis, comparing hemofiltration to hemodialysis.[6] All studies included ICU patients, and the review examined mortality, renal replacement therapy dependence, filter life and organ dysfunction, and other clinical outcomes.
    - One of the 200 randomly selected studies we examined CRRT, for an expected total of four studies.[18]
  - 2.a.ii. Continuous versus extended daily or intermittent hemofiltration and/or hemodialysis
    - A new evidence review *would be duplicative*. We identified a 2010[9] and a 2013[8] review comparing CRRTs to EDD or IHD on mortality, kidney recovery, renal replacement therapy dependence, and fluid removal.
    - From the randomly selected 200 studies we examined, three[19,21,23] comparing continuous, extended daily, and intermittent HD, for an expected total of 11 studies.
  - 2.a.iii. Among peritoneal dialysis modalities or compared to hemofiltration and/or hemodialysis
    - A new evidence review *would be duplicative*. We identified a 2012 Cochrane review,[7] a 2013 review,[5] and a Cochrane protocol (anticipated completion date February 2017)[10] examining PD alone or as compared to HD. While the Cochrane review includes only one study comparing PD to CEPD, and the 2013 review, which compares PD to CRRT, IHD, and DHD, only examines mortality, the in-process review will include studies comparing PD with and without supportive treatment to HD (including all different modalities of IHD or CRRT) with and without supportive treatment, as well as different modalities of PD on outcomes such as kidney function, duration of renal replacement therapy and laboratory indices.
    - From the randomly selected 200 studies we examined, two[20,22] examined harms or costs associated with PD or as compared to HD, for an expected total of 8 studies.

- Key Question 2b. Harms and Costs of Renal Replacement Modalities
    - 2.b.i. Among hemodialysis (HD) continuous renal replacement therapies
        - A new evidence *would not be duplicative*. We identified a 2012 meta-analysis, comparing hemofiltration to hemodialysis on organ dysfunction and filter failure among ICU patients.[6] No other harms were examined. We identified no reviews examining costs.
        - From the 200 randomly selected studies we examined, we identified no examining harms or costs associated with CRRT.
    - 2.b.ii. Continuous versus extended daily or intermittent hemofiltration and/or hemodialysis
        - A new evidence *would not be duplicative*. We identified one review comparing EDD to CRRT on episodes of vasopressure escalation and cost. No other harms were examined.
        - From the randomly selected 200 studies we examined, four[23-26] compared harms or costs associated with continuous, extended daily, or intermittent HD, for an expected total of 14 studies.
    - 2.b.iii. Among peritoneal dialysis modalities or compared to hemofiltration and/or hemodialysis
        - A new evidence review *would be duplicative*. We identified a 2012 Cochrane review,[7] a 2013 review,[5] and an in-process Cochrane review (anticipated completion date February 2017)[10] examining PD alone or as compared to HD. Although the existing review includes only one study comparing PD to CEPD on time and cost, the in-process review will include studies comparing PD with and without supportive treatment to HD (including all different modalities of IHD or CRRT) with and without supportive treatment, as well as different modalities of PD on outcomes related to cost, and adverse events such as including bleeding, peritonitis, respiratory insufficiency, and hypoalbuminemia.
        - From the 200 randomly selected studies we examined, we identified no studies examining harms or costs associated with PD or as compared to HD.
- Key Question 3a. RRT Dose
    - A new evidence review *would not be duplicative*. We identified a 2011 evidence review[14] comparing high to low intensity CRRT in critically ill patients. No other outcomes were examined
    - From the 200 randomly selected studies we examined, we identified three[29,30,34] studies examining dose, for an expected total of 11 studies.
- Key Question 3b. Timing/Initiation of RRT
    - A new evidence review *would likely be duplicative*. We identified three completed reviews[10,13,16] examining timing/initiation, with congruent findings examining the topic.
    - One[32] of the 200 randomly selected studies we examined related to the timing/initiation of renal replacement therapy, for an expected total of four studies.
- Key Question 3c. Fluid Composition
    - A new evidence review comparing bicarbonate vs. lactate-buffered fluids *would be duplicative*. We identified both a 2015 Cochrane[15] and another (2014) review[12] comparing bicarbonate to lactate-buffered solutions on outcomes such as serum creatinine, hypotensive episodes, and mortality. (Table 6). However, a new

review examining anticoagulants *would not be duplicative*. We identified no completed or in-process reviews.
    - From the 200 randomly selected studies we examined, we identified three[28,31,33] studies examining fluid composition, for an expected total of 11 studies.
- Key Question 3d. Time/Length of RRT Session
    - A new evidence review *would not be duplicative*. We identified no completed or in-process reviews covering the scope of the key question.
    - One[27] of the 200 randomly selected studies we examined related to time/length of RRT session, for an expected total of four studies.
- Key Question 4. Predictors of Renal Outcomes and Mortality
    - A new evidence review *would not be duplicative*. We identified no relevant completed or in-process evidence reviews.
    - We identified seven studies related to predictors, from the randomly selected 200 we examined, for an expected total of 25 relevant studies.
- Key Question 5a. Optimal Frequency/Parameters of Laboratory Monitoring and Clinical Assessment
    - A new evidence review *would not be duplicative*. We identified no relevant completed or in-process reviews.
    - From the 200 randomly selected studies we examined, we identified two studies examining optimal frequency/parameters for an expected total of seven relevant studies.
- Key Question 5b. Comparing AKI-D to ESRD on Optimal Frequency/Parameters of Laboratory Monitoring and Clinical Assessment
    - A new evidence review *would not be duplicative*. We identified no relevant completed or in-process reviews comparing individuals with AKI-D to individuals with ESRD on optimal frequency/parameters.
    - From the 200 randomly selected studies we examined, no studies compared individuals with AKI-D to individuals with ESRD on optimal frequency/parameters.

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Appendices

Appendix A: Selection Criteria Summary

Appendix B: Search for Existing Guidance

Appendix C: Search Strategy

Appendix D: Search for Existing Evidence Results

Appendix A: Selection Criteria Summary

Selection Criteria	Supporting Data
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this topic represents a health care drug and intervention available in the U.S.
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	The focus of this review is on effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible. Yes, it is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, AKI-D occurs in 1-2% of hospitalized patients and 6-7% of critically ill patients.[1] AKI-D is associated with a mortality rate of 33% among in-hospital patients and 50-60% among ICU patients.[1] Among survivors of AKI-D, between 10-30% require dialysis post-discharge.[2]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Although the incidence of AKI-D has been increasing at a rate of 10% per year, patients with AKI-D face considerable barriers to receiving appropriate treatment.[2] A 2012 clarification of Centers for Medicare and Medicaid Services (CMS) policy prohibited reimbursement for AKI-D treatment at End Stage Renal Disease (ESRD) facilities.[2] However in 2015, Congress amended the Social Security Act to permit reimbursement for AKI-D treatment at ESRD facilities beginning in Jan 2017.
2c. Represents important uncertainty for decision makers	This topic may represent important uncertainty for decision makers. Observational studies suggest that adverse outcomes may be mitigated by reducing the severity and duration of AKI-D.[1] However, little is known about whether particular management strategies or treatments facilitate renal recovery among AKI-D patients.[1] Currently no guidelines or established metrics exist for the treatment of AKI-D in outpatient settings, and the needs of this population is different than patients with ESRD.[3]
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this nomination addresses both benefits and potential harms of treatments for AKI-D.

2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, AKI is associated with increased mortality, length of stay, and costs for hospitalized patients.[4] Treatment for AKI accounts for 5% of all hospital expenditures in the U.S. each year, which is equivalent to approximately $10 billion.[4]
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	• Key questions 1a/b, 2a, 4, and 5a/b would not be redundant. We identified no current or in-process evidence reviews. • Key Question 2b. A new evidence review on the *harms among CRRTs* would not be redundant. While we identified a 2012 meta-analysis examining organ dysfunction and filter failure, other known potential harms were not examined.[9] Similarly, a new evidence review comparing the *harms associated with continuous to extended daily or intermittent renal replacement therapies* would not be redundant. We identified a 2015 review examining vasopressure escalation and cost. No other harms were examined.[6] A review examining harms associated with PD or comparing PD to HD would be redundant. We identified 2012 Cochrane review,[5] a 2013 review,[7] and a Cochrane protocol (anticipated completion date February 2017).[10] Although the Cochrane review [5] compares only PD to CEPD on time and cost, and the other review examines only peritonitis, the in-process review will include studies comparing PD with and without supportive treatment to HD (including all different modalities of IHD or CRRT) with and without supportive treatment, as well as different modalities of PD on outcomes related to cost, and adverse events such as including bleeding, peritonitis, respiratory insufficiency, and hypoalbuminemia.[10] • Key Question 3. A new evidence review *comparing early to late initiation of RRT* would likely be redundant. We identified three existing reviews[11-13] with congruent findings examining the topic. In addition, a new evidence review *comparing dialysis fluid composition* (bicarbonate vs. lactate-buffered) would likely be redundant. We identified two existing reviews, one examining continuous haemodiafiltration or haemofiltration,[14] and the other PD.[15] However, new evidence reviews examining dose, anticoagulant methods, or time/length would not be redundant.
4. Impact of a New Evidence Review	

4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes, the standard of care is unclear due to lack of research on patients with AKI-D in outpatient settings due to existing CMS policies excluding patients with AKI-D from reimbursement in outpatient settings.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	It is unclear whether there is variation in practice for patients with AKI-D, due in part to the likelihood that patients with AKI-D may currently be classified as ESRD early to enable reimbursement for outpatient dialysis. It is also unclear how the standards of care related to outpatient dialysis should differ in patients with AKI-D as compared to patients with ESRD.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	• Key Question 1. From the 200 randomly selected studies we examined, two[16,17] were relevant, for an expected total of seven relevant studies. • Key Question 1b. One[17] of the 200 randomly selected studies we examined was relevant to the key question, for an expected total of four relevant studies. • Key Question 2a. Seven[18-24] of the 200 randomly selected studies were relevant, for an expected total of 25 relevant studies. • Key Question 2b. Five[18,22,25-27] of the 200 randomly selected studies we examined were relevant, for an expected total of 18 relevant studies. • Key Question 3. Of the 200 randomly selected studies we examined, nine[18,28-35] were relevant, for an expected total of 32 relevant studies. • Key Question 4. We identified seven[18,22,36-39] relevant studies from the randomly selected 200 we examined, for an expected total of 25 relevant studies. • Key Question 5a. From the 200 randomly selected studies we examined, we identified two[41,42] relevant studies, for an expected total of seven relevant studies. • We identified no studies related to key question 5b.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes, this topic will impact clinical decision-making on how to best treat AKI-D to facilitate renal recovery. This topic will also help to inform payer reimbursement policies for outpatient AKI-D treatments.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes, CMS will use the systematic review to inform policy on reimbursement for outpatient AKI-D treatments.

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Appendix B. Search for Existing Guidance

Listed below are the sources searched and results of our search for existing guidance. A research librarian conducted the search and selected potentially relevant evidence based on the key question in the nomination and the associated PICOTS. An investigator reviewed each of the links to evidence below for inclusion. The links below do not represent the evidence selected for inclusion (see main topic brief).

Acute Kidney Injury	
Source	**Evidence**
Search for Duplication: Search Conducted January 8, 2016	
AHRQ and Other Federal Products	
AHRQ: Evidence reports and technology assessments, USPSTF recommendations, and related DEcIDE projects, and Horizon Scan ▪ EPC Program Reports and In-Process Topics: http://www.ahrq.gov/research/findings/evidence-based-reports ▪ Archived EPC Program Reports: http://archive.ahrq.gov/clinic/epcarch.htm ▪ EHC Program Reports: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/ ▪ Technology Assessments: http://www.ahrq.gov/clinic/techix.htm ▪ USPSTF Reports: http://www.uspreventiveservicestaskforce.org/uspstopics.htm ▪ USPSTF In-Process Topics: http://www.uspreventiveservicestaskforce.org/Page/Name/topics-in-progress ▪ DEcIDE Projects: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/ ▪ AHRQ Horizon Scanning (click on status update reports): http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=881 ▪ AHRQ-funded projects that may be conducting systematic reviews (1. Under TEXT SEARCH, enter in key text terms, select projects and publications; 2.Under PROJECT DETAILS and then under “Agency/Institute/Center,” select Agency for Healthcare Research and Quality and check the boxes for “Admin” and “Funding”; 3) Scroll to the end and click on SUBMIT	• Smad-pathway activating peptide (THR-184) for treatment of acute kidney injury after cardiac surgery https://effectivehealthcare.ahrq.gov/ehc/products/393/880/AHRQ-Healthcare-Horizon-Scanning-Status-Update-151130.pdf

QUERY http://projectreporter.nih.gov/reporter.cfm	
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program ▪ HSR&D ESP Reports and In-Progress Topics: http://www.hsrd.research.va.gov/publications/esp/ ▪ PBM Recommendations: http://www.pbm.va.gov/PBM/clinicalguidance/clinicalrecommendations.asp ▪ PBM Drug Class Reviews: http://www.pbm.va.gov/PBM/clinicalguidance/drugclassreviews.asp Other PBM products may be reviewed if deemed necessary; however, these are generally not reviewed for most topics unless the nomination is closely linked to the VA population and VA policies: http://www.pbm.va.gov/ClinicalGuidance.aspx	
Cochrane and Other Systematic Reviews	
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/	• Chemotherapy with or without plasmapheresis in acute renal failure due to multiple myeloma: A meta-analysis http://europepmc.org/abstract/med/25816886. • Thyroid hormones for acute kidney injury http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006740.pub2/epdf/standard • Diuretics in acute kidney injury http://europepmc.org/abstract/med/18636060 • Atrial natriuretic peptide for preventing and treating acute kidney injury http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006028.pub2/epdf/standard • High-dose methotrexate-induced nephrotoxicity in patients with osteosarcoma http://onlinelibrary.wiley.com/doi/10.1002/cncr.20255/full • Use of dopamine in acute renal failure: A meta-analysis http://journals.lww.com/ccmjournal/Abstract/2001/08000/Use_of_dopamine_in_acute_renal_failure__A.5.aspx • Extended daily dialysis versus continuous renal replacement therapy for acute kidney injury: A meta-analysis http://www.sciencedirect.com/science/article/pii/S0272638615005004

	• Bicarbonate- versus lactate-buffered solutions for acute continuous haemodiafiltration or haemofiltration http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006819.pub2/epdf/standard • Bicarbonate versus lactate solutions for acute peritoneal dialysis http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007034.pub2/epdf/standard • Use of peritoneal dialysis in AKI: A systematic review http://cjasn.asnjournals.org/content/8/10/1649.short • Hemofiltration compared to hemodialysis for acute kidney injury: Systematic review and meta-analysis http://link.springer.com/article/10.1186/cc11458 • Tidal versus other forms of peritoneal dialysis for acute kidney injury http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007016.pub2/epdf/standard • A systematic review of continuous renal replacement therapy and intermittent haemodialysis in management of patients with acute renal failure http://onlinelibrary.wiley.com/doi/10.1111/j.1440-1797.2008.00966.x/full • Biocompatible hemodialysis membranes for acute renal failure http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005283.pub2/epdf/standard • Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: A meta-analysis http://journals.lww.com/ccmjournal/Abstract/2008/02000/Continuous_versus_intermittent_renal_replacement.34.aspx • Renal replacement therapy in patients with acute renal failure: A systematic review http://jama.jamanetwork.com/article.aspx?articleid=181491 • High cut-off point membranes in septic acute renal failure: A systematic review http://europepmc.org/abstract/med/18203064 • Intermittent versus continuous renal replacement therapy for acute renal failure in adults http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003773.pub3/epdf/standard • Influence of dialysis membranes on outcomes in acute renal failure: A meta-analysis

	http://www.sciencedirect.com/science/article/pii/S008525381548740X • Effect of biocompatibility of hemodialysis membranes on mortality in acute renal failure: A meta-analysis http://europepmc.org/abstract/med/12005243 • Acute renal failure in the intensive care unit: A systematic review of the impact of dialytic modality on mortality and renal recovery http://www.sciencedirect.com/science/article/pii/S0272638602500251 • A primer on continuous renal replacement therapy for critically ill patients http://aop.sagepub.com/content/32/3/362.short • Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: A systematic review and meta-analysis http://link.springer.com/article/10.1007/s00134-013-2864-5 • Early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury after cardiac surgery: a systematic review and meta-analysis http://www.sciencedirect.com/science/article/pii/S105307701300699X • Timing of initiation of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis http://www.tandfonline.com/doi/abs/10.3109/0886022X.2011.647371#.VsdfJub0T08 • Renal replacement therapies after abdominal aortic aneurysm repair--a review http://www.acta-clinica.kbcsm.hr/arhiva/Acta2011/Acta3/15.pdf • Intensity of continuous renal replacement therapy in acute kidney injury in the intensive care unit: a systematic review and meta-analysis http://ves.sagepub.com/content/early/2011/05/24/1538574411407935.short • A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis http://link.springer.com/article/10.1186/cc10061#page-1 • Intensive- vs less-intensive-dose continuous renal replacement therapy for the intensive care unit-related acute kidney injury: a meta-analysis and systematic review http://www.sciencedirect.com/science/article/pii/S0883944110001589 • The dose of continuous renal replacement therapy for acute renal

	failure: a systematic review and meta-analysis http://www.tandfonline.com/doi/abs/10.3109/08860221003728739 • High-dose renal replacement therapy for acute kidney injury: Systematic review and meta-analysis http://journals.lww.com/ccmjournal/Abstract/2010/05000/High_dose_renal_replacement_therapy_for_acute.18.aspx • Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis http://www.sciencedirect.com/science/article/pii/S0272638608008299 • Relationship of cystatin-c change and the prevalence of death or dialysis need after acute kidney injury: A meta-analysis http://onlinelibrary.wiley.com/doi/10.1111/nep.12312/full
PubMed Health	Identified items already identified previously
Systematic Reviews and Meta-analyses (PubMed/MEDLINE)	
NHS Evidence http://www.evidence.nhs.uk/default.aspx	
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/ (Search HTA tab results)	• Effect of atrial natriuretic peptide, ANP, on the need for dialysis, when used as treatment or prevention of acute renal failure in intensive care • Continuous renal replacement therapy (CRRT) versus sustained low-efficiency daily dialysis (SLED) for adults with non-trauma-related acute renal failure http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32010000837&UserID=0 • Continuous renal replacement therapy in adult patients with acute renal failure: systematic review and economic evaluation http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32007000540&UserID=0 • Citrasate dialysate for patients with chronic or acute renal failure requiring long-term haemodialysis: horizon scanning technology briefing http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32006001097&UserID=0
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/	• Peritoneal dialysis for acute kidney injury [Cochrane Protocol] http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015024054
Search for Original Research: Search Conducted January 8, 2016	

Published primary research studies PubMed/MEDLINE Other applicable databases (e.g., CINAHL, PsycINFO)	
Clinical trials ClinicalTrials.gov http://clinicaltrials.gov/ct2/search	• https://clinicaltrials.gov/ct2/results?term=dialysis&cond=%22Acute+Kidney+Injury%22

Appendix C. Search Strategy

Search Strategy PubMed Searched January 8, 2016

((((((((("Water-Electrolyte Balance"[Mesh]) OR "Blood Pressure"[Mesh]) OR "Anemia"[Mesh]) OR "Nutritional Status"[Mesh]) OR "Bone Diseases"[Mesh])) OR ((fluid[Title/Abstract] OR "blood pressure"[Title/Abstract] OR anemia[Title/Abstract] OR nutrition*[Title/Abstract] OR bone[Title/Abstract]))))) AND ((((("Renal Dialysis"[Mesh]) OR dialysis[Title/Abstract])) AND (("Acute Kidney Injury"[Mesh]) OR (("acute kidney injury"[Title/Abstract] OR "acute kidney injuries"[Title/Abstract] OR AKI[Title/Abstract])))))) AND "therapy" [Subheading])
OR
((((((modality[Title/Abstract] OR peritoneal[Title/Abstract] OR intermittent[Title/Abstract] OR continuous[Title/Abstract] OR length[Title/Abstract] OR frequency[Title/Abstract]))) AND "last 10 years"[PDat] AND Humans[Mesh] AND adult[MeSH])) AND ((((("Renal Dialysis"[Mesh]) OR dialysis[Title/Abstract])) AND (("Acute Kidney Injury"[Mesh]) OR (("acute kidney injury"[Title/Abstract] OR "acute kidney injuries"[Title/Abstract] OR AKI[Title/Abstract])))))
OR
(((((((("Renal Dialysis"[Mesh]) OR dialysis[Title/Abstract])) AND (("Acute Kidney Injury"[Mesh]) OR (("acute kidney injury"[Title/Abstract] OR "acute kidney injuries"[Title/Abstract] OR AKI[Title/Abstract])))))) AND "therapy" [Subheading]))))) AND ((("Arteriovenous Fistula"[Mesh]) OR Transplants"[Mesh]) OR ("arteriovenous fistula"[Title/Abstract] OR graft[Title/Abstract] OR transplantation[Title/Abstract]))) AND ((time[Title/Abstract] OR timing[Title/Abstract]))
OR
(((((((("Renal Dialysis"[Mesh]) OR dialysis[Title/Abstract])) AND (("Acute Kidney Injury"[Mesh]) OR (("acute kidney injury"[Title/Abstract] OR "acute kidney injuries"[Title/Abstract] OR AKI[Title/Abstract])))))) AND "therapy" [Subheading]))))) AND ((("Monitoring, Physiologic"[Mesh]) OR (monitoring[Title/Abstract] OR assessment[Title/Abstract]))) AND ((frequency[Title/Abstract] OR often[Title/Abstract] OR timing[Title/Abstract]))

Filters activated: published in the last 10 years, Humans.

Search Results:

Systematic Reviews	25
http://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/49406308/public/ AKI SR.txt	
Randomized Controlled Trials	285
http://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/49406323/public/ AKI RCT.txt	
All others	447
http://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/49406331/public/ AKI other.txt	

Appendix D: Search for Existing Evidence Results

Table 1. Search for Existing Evidence Results: Overall

Nomination: Acute Kidney Injury

	Search Yield	Included/ Reviewed	Percent Included	Expected Total Included Studies
MEDLINE All Results	718	25/200	12.5%	90
MEDLINE Clinical trials[1]	230	16/67	24%	55
MEDLINE Evidence Reviews[2]	34	2/11	18%	6
MEDLINE Other Studies	454	7/122	6%	27

Note. If results eligible for review was > 200, we review a random sample of 200, and calculate the expected number of total studies.

[1] We use the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE.http://handbook.cochrane.org/chapter_6/box_6_4_b_cochrane_hsss_2008_sensprec_pubmed.htm

[2] We use The Systematic Reviews Subset in PubMed http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html

Table 2. Expected Yield by Key Question

Nomination: Acute Kidney Injury
Total Search Yield: 718

	Included/Reviewed	Percent Included	MEDLINE All Results (718)	MEDLINE Clinical trials[1](230)	MEDLINE Evidence Reviews[2](34)	MEDLINE Other Studies (454)
All KQs	30/200	12.5	90	55	6	27
KQ 1a	0/200	0%	0	0	0	0
KQ 1b	0/200	0%	0	0	0	0
KQ 2a	6/200	3%	22	7	1	14
KQ 2b	4/200	2%	14	5	1	9
KQ 3	9/200	4.5%	32	10	1	20
KQ 4	7/200	3.5%	25	8	1	16
KQ 5a	2/200	1%	7	2	0	5
KQ 5b	0/200	0%	0	0	0	0