Evidence-based Practice Center Systematic Review Protocol

Project Title: *End-stage Renal Disease in the Medicare Population*

Initial publication date: June 6, 2019

Amendment Date(s) if applicable: June 26, 2019

(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

Introduction

Over 100,000 patients (children and adults) reach end-stage renal disease (ESRD) every year (incident patients) and there are approximately 500,000 prevalent ESRD patients on dialysis.[3] The ESRD population is expected to expand and the latest projections suggest that by 2030, up to 1,259,000 patients will be on maintenance dialysis.[4] In 2016, 90 percent of Medicare ESRD patients on dialysis were treated with hemodialysis (N=457,957). Of the patients treated with hemodialysis, 98% were treated using in-center hemodialysis (generally prescribed thrice weekly) and the remaining 2% were undergoing home hemodialysis (3-5 times per week or nocturnal). Very few of the in-center hemodialysis patients are treated with thrice weekly in-center overnight hemodialysis (nocturnal hemodialysis, 7-8 hours per treatment).[3] More frequent dialysis is generally prescribed at home, and became feasible after the availability of the NxStage home hemodialysis machine in 2005; in 2014, 8,600 patients were treated with home hemodialysis, a 4-fold increase since 2000.[5]

Despite many advances in general medical care, dialysis technology, anemia and bone-mineral metabolism management, and almost universal attainment of dialysis adequacy targets (Kt/Vurea), 25 percent of incident dialysis patients do not survive the first year of dialysis; median survival is only 4 years, and 5-year survival is about 40 percent.[3] Quality of life (QOL) on dialysis is poor with most dialysis patients experiencing uremic symptoms such as fatigue, poor appetite, malnutrition, poor sleep quality, restless legs, sexual difficulties, frailty, and cognitive impairment.[9-11] QOL is often valued by patients even more than survival,[12-14] but it remains understudied.

Decisional Challenges

The major benefit of more frequent and longer dialysis treatments seems to be from volume removal; more frequent dialysis in the Frequent Hemodialysis Network (FHN) Trials led to an average of 1.6 L per week extra ultrafiltration achieved by 2-3 extra treatments per week,[16] contributing to better blood pressure control and less antihypertensive medication use. Although greater removal of (unknown) uremic toxins was hypothesized as a potential benefit of more frequent and/or longer hemodialysis, a recent study from the FHN cohort reported an average lowering of only 15 percent in the levels of 107 known uremic solutes.[17] However, more frequent dialysis is not risk free. Each dialysis treatment can be associated with potential risks, including infection,

intradialytic hypotension (and its complications including myocardial stunning), and infectious events. These considerations contribute to decisional challenges regarding dialysis frequency and treatment time (duration).

Further decisional conflicts result from the Medicare reimbursement policies which are tied to per treatment urea clearance (Kt/V) rather than to the original intent of dialysis, rehabilitation of uremic patients to a fully functional status. Healthcare system and payer decisional conflicts arise when approval is sought for more frequent dialysis, in patients considered "adequately" dialyzed based on Kt/V targets. It is unclear how more frequent dialysis could impact the total cost of care. While the cost of dialysis treatments will increase with more frequent dialysis and there could be higher dialysis access-related costs, would it be offset by lower risk of hospitalizations, and lower long-term cardiovascular disease morbidity?

Several key factors should be considered to contextualize the observed effects of more frequent dialysis. These factors include heterogeneity of patients treated with dialysis, accuracy of ascertainment of risk predictors and outcomes, the clearance provided by hemodialysis, and the benefits, risks, and burden experienced by patients treated with hemodialysis. There is marked heterogeneity in the ESRD patients treated with hemodialysis due to differences in age, comorbidity, social determinants of health, cause of ESRD, and goals of dialysis. Dialysis registry data often cannot distinguish between these subgroups and clinical trials may be affected by selection bias related to the marked heterogeneity in patients with ESRD. Dialysis studies that rely solely on registry or electronic health record data also risk misclassification of exposure and outcome variables, such as blood pressure where the errors in measurements could be as high as 15 mm Hg.[22] This information bias is likely to vary, with patients having multiple comorbidities likely to experience greater errors.

Finally, patient perspective is essential to put outcome data in context. Each dialysis treatment takes 4-6 hours away from a work day and is associated with a small but incremental risk of vascular access complications, blood stream infections, cramping during dialysis, and post-dialysis fatigue. These might balance out with less uremic symptoms, greater energy, and ability to maintain employment. A systematic review on the comparison between more frequent or longer hemodialysis and standard hemodialysis will help identify the key areas of focus for future studies while addressing questions that can direct quality improvement efforts to improve patient-centered outcomes including survival and QOL.

We aim to conduct a technology assessment on clinical outcomes and QOL in ESRD patients treated with hemodialysis, focusing on the effect of more hemodialysis (higher frequency or longer time) on clinical outcomes. In addition to identifying evidence gaps that need to be addressed in future research, our critical appraisal of evidence will identify practice gaps so that quality improvement initiatives can focus on where clinical practice lags behind the evidence.

II. The Key Questions (KQ)s

The KQs were posted for public comment between July 5 and August 17, 2019. Comments were received from federal agency officials, advocacy groups representing patients and providers, and a dialysis center. Commenters were in general satisfied with the questions and agreed that the review should include information on subgroups, include data from both randomized controlled trials (RCTs) and observational studies, and include all quality of life tools that were validated in dialysis populations. As defined below, the methods for this project have ensured that all hemodialysis populations evaluated in studies on frequency and duration of hemodialysis are included and their characteristics will be recorded. In summary, the public comments did not substantially change the key questions, and we have made clear throughout the protocol what information will be included.

KQ 1:
In studies of frequency and duration of hemodialysis in non-institutionalized individuals, what are the characteristics of the patients and dialysis modality (including home or dialysis center setting and flow rate)? What is the length of follow up on patients in the studies? How does this compare to the general population of patients on dialysis?

KQ 2:
In hemodialysis patients, does more frequent hemodialysis (more than 3 times a week) improve objective outcomes (including hypertension control, mortality, QOL) over the long term (more than 6 months) compared to usual hemodialysis frequency (3 times a week)? What is the impact of patient characteristics and modality of dialysis used in the studies on outcomes?

KQ 3:
In hemodialysis patients, does extended hemodialysis duration (daytime, 4 or more hours per session, or nocturnal, overnight) improve objective outcomes (including hypertension control, mortality, QOL) over the long term (more than 6 months) compared to usual length hemodialysis duration (less than 4 hours)? What is the impact of patient characteristics and modality used in the studies on outcomes?

Table 1. Explanation of duration and frequency of hemodialysis under consideration for KQs 1-3.

		Duration (hours per session)	
		Less than 4 hours	4 hours and more
Frequency (treatment N) per week	3 sessions	9-<12* hours per week	>= 12 hours per week
	4 or more sessions	9- to <16** hours per week	>=16 hours per week

* Usual care involves 3 sessions per week with 3-4 hours per session.
** The duration of each dialysis session is generally shorter when dialysis is done more frequently.

KQ 4:
What instruments have been used to measure QOL in studies of people with ESRD treated by dialysis?

Subquestion 4a: What are the psychometric properties of instruments used to measure QOL in studies of people with ESRD treated by dialysis?

Subquestion 4b: What is the minimal clinically important difference for instruments used to measure QOL in studies of people with ESRD treated by dialysis?

Subquestion 4c: How have instruments used to measure QOL in studies of people with ESRD treated by dialysis been validated?

Subquestion 4d: What is the impact of placebo effect in studies used to measure QOL in people with ESRD treated by dialysis and what study designs are needed to mitigate the impact?

Population(s)

- All KQs: US ESRD Medicare population (non-institutionalized)
- KQ 1: Adults and children with ESRD on hemodialysis (no age restriction)
- KQs 2 and 3: Adults and children with ESRD on hemodialysis
- KQ 4: Adults and children with ESRD treated with any dialysis or other non-transplant treatment.

Interventions

- KQ 1: Different frequency or duration of hemodialysis
    - KQ 2: More frequent hemodialysis (3 versus > 3 sessions/week)
- KQ 3: Increased duration of hemodialysis sessions (12 hours versus > 12 hours per week; or daytime versus night time)
- KQ 4: For this question, we will include studies of QOL in people with ESRD receiving any type of dialysis.
- We will abstract data on all home hemodialysis machines (2008K@Home Hemodialysis Machines, NxStage® System One, NxStage® System S) as well as all devices used in-center (a large variety of machines used in center exist and all will be considered for data collection).

Comparators (see Table 1)

- KQs 1 and 4: Usual care (3 times per week and 3-4 hours per treatment).
- KQ 2: More frequent hemodialysis (> 3 session/week); usual care
- KQ 3: Increased duration of hemodialysis sessions (≥ 12 hours per week, or nocturnal, overnight); usual care

Outcomes

- KQ 1: Not applicable (see Appendix A for a list of the patient characteristics that will be considered for this KQ)
- KQs 2 and 3:
    - Final health outcomes (see Appendix B for a detailed list of outcomes): clinical outcomes including cardiovascular events, hospitalizations, QOL, pregnancy outcomes, and mortality
    - Adverse events (see Appendix B for a detailed list of outcomes): intradialytic hypotension, access complications, loss of residual kidney function, infectious events, myocardial stunning hospitalizations, and patient and caregiver burden

- Intermediate outcomes (see Appendix B for a detailed list of outcomes): metabolic/inflammatory control, blood pressure control, dialysis recovery time
- KQ 4:
  - Instruments used to measure QOL in dialysis patients
  - Psychometric properties of these instruments
  - Minimal clinically important difference for these instruments
  - Validation of these instruments
  - Placebo effect in studies of QOL in dialysis patients and what study designs are needed to mitigate the impact

Timing

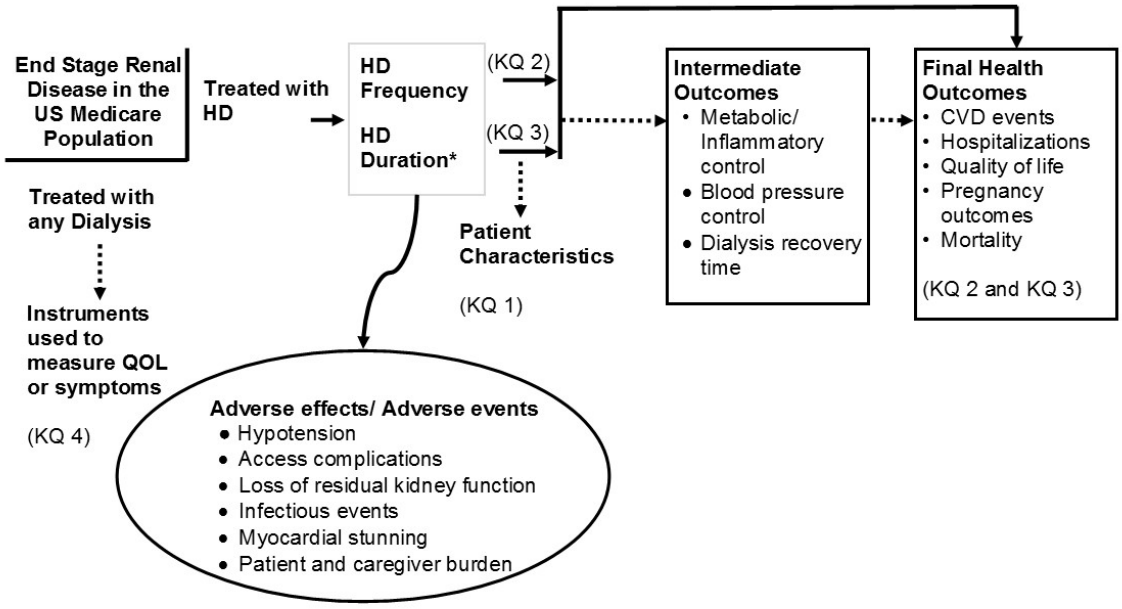
- KQs 1-3: Minimum of 6 months of follow-up after the intervention is initiated
- KQ 4: no minimum follow-up

Setting

- Home dialysis, and dialysis center (Non Institutionalized)

III. Analytic Framework

Analytic Framework



CVD=cardiovascular disease; HD=hemodialysis; KQ=key question; QOL=quality of life
* treatment decision may be one-time, or varies over time.

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

We will follow the above defined populations, interventions, comparators, outcomes, timing, setting (PICOTS) framework for the key questions in developing the criteria for inclusion of studies in the technology assessment. We will include all studies of the non-

institutionalized United States ESRD Medicare population (both adults and children). Patients must be receiving hemodialysis to be included in KQ 1 thru 3.

For KQ1, we will include all study designs that include a comparison group RCTs, non-RCTs, prospective and retrospective cohort studies with a comparison group) on frequency or duration of hemodialysis over the long term (more than six months).

For KQ2, we will include all study designs that include a comparison group (RCTs, non-RCTs, prospective and retrospective cohort studies with a comparison group) on frequency of hemodialysis over the long term (more than six months).

For KQ3, we will include all study designs that include a comparison group (RCTs, non-RCTs, prospective and retrospective cohort studies with a comparison group) on duration of hemodialysis over the long term (more than six months).

KQ4 is not a comparative question and will include all studies on United States ESRD patients receiving any form of dialysis or other therapy excluding transplant. Main outcomes of interest are detailed in Appendix B. We will abstract this information as it is presented, focusing on all QOL-related outcomes.

For all KQs, we will exclude studies that are not conducted in a home dialysis or in-center setting.

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

Two comprehensive search strategies will be developed: one for KQs 1 thru 3, and the other for KQ 4. Search strategies will be developed in PubMed and will be adapted for and applied to EMBASE, and the Cochrane Library (see Appendix C). Searches of all databases will be limited to articles published in 2005 to present for KQ 1 thru 3; no date limitation will be used for the KQ 4 search. The date limitation is driven by the fact that in the present era, more frequent dialysis is generally prescribed at home, and became feasible after the availability of the NxStage home hemodialysis machine in 2005. [23] These databases were selected based on internal expert opinion that they would identify most of the relevant literature on this topic. Searches will be updated when the draft report is submitted for peer review. We will hand search the references of relevant systematic reviews to identify additional relevant articles.

We will search the following grey literature sources for all KQs to identify evidence that may not appear in the peer reviewed literature, or is on-going: ClinicalTrials.gov, and SCOPUS, using the same date restrictions used for the published literature search (2005 to present). We will also conduct a search of abstracts of the following professional meetings for the last 3 years: American Society of Nephrology Kidney Week, [24] and the National Kidney Foundation Clinical Meetings.[25] The purpose of the grey literature search is to identify additional sources of data that will be included in the final technology assessment as well as to estimate potential publication bias.

KQ 4 addresses identification of tools used to assess QOL in individuals with ESRD on any form of dialysis. We will conduct additional searches of the Patient Reported Outcomes Measurement Information System (PROMIS®) Health Measures website[26] for information on patient reported outcome measures (PROMs) that have or can be applied

to the United States ESRD populations. The PROMIS® website provides information on the methodology used for developing its measures, and for applicable PROMs we will use this site to obtain information on psychometric properties.

Due to the projected volume of literature for all KQs, we will screen titles first, then screen abstracts for relevance to the KQs based on the above inclusion/exclusion criteria. Titles and abstracts will be screened independently by two reviewers. Screeners (both title and abstract) will include senior team members (extensive relevant clinical background and/or extensive experience in systematic review methods and application) and research assistants with training in clinical medicine and epidemiology. The research assistants will always be paired with a senior team member to screen titles and abstracts. Inclusion at the title screening level will be liberal; if a single reviewer believes an article may contain relevant information based on title, the article will move to the next level (abstract) for further screening. Abstracts require that both reviewers agree on either inclusion or exclusion. Disagreements that cannot be resolved by the two reviewers will be resolved by the internal experts.

Full text articles included at the abstract level will be reviewed independently by two reviewers (same groups as above for screening: senior team members and research assistants) and require agreement between the reviewer for either inclusion or exclusion. Disagreements that cannot be resolved by the two reviewers will be resolved by a third expert member of the team.

At random intervals during screening, quality checks by senior team members will occur to ensure that inclusion/exclusion criteria are consistently applied during screening.

We will evaluate existing systematic reviews on the topic to determine the extent to which they address our specific KQs (1-3). If a high quality (based on the AMSTAR)[27] systematic review fully addresses one of our specific KQs (1-3), we will attempt to incorporate that information into our review. Our ability to incorporate a previous review into our review will depend on whether the methods of the review are consistent with our protocol. At a minimum, we will check to make sure that studies included in previous reviews of the topic are taken into consideration in our review.

KQ 4 will be approached in a different manner. We will search the literature for all study designs. We anticipate that research has already been conducted and synthesized on QOL measures in the United States ESRD population. We will use the information provided in reviews to provide details on the psychometric properties, minimal clinically important difference, and placebo effects. We will supplement information in the systematic reviews with evidence in the primary literature.

Data Abstraction and Data Management

We will use Distiller SR (Evidence Partners, Ottawa, Canada) to manage the screening process. Distiller SR is a web-based data management program that manages all levels of the review process. All applicable articles identified by the search process will be uploaded to the system.

Data from applicable articles will be abstracted into DistillerSR. At the end of the project, data will be added to the Systematic Review Data Repository™, a web-based data

repository for archiving. The data will be exported from DistillerSR to create detailed evidence and summary tables.

We will use a systematic approach to extract the data to minimize the risk of bias or errors in this process. We will create standardized forms for data abstraction, which will be pilot tested internally by the team. By creating standardized forms for data extraction, we will maximize consistency in identifying pertinent data available for synthesis. Each article will undergo double review by study investigators for data abstraction. In all cases, data will be abstracted first by a research assistant. If we experience a large volume of studies to be abstracted, the review methodologists will also work as first level data abstractors. A senior level reviewer (clinician or experienced systematic review methodologist) will confirm the first reviewer's abstraction for completeness and accuracy. A third reviewer will randomly audit a sample assessed by the first two reviewers to ensure consistency in the data abstraction. Articles referring to the same study will be abstracted on a single review form if reporting on the same data, or on separate forms if necessary, with clear information provided that the results should be interpreted as from the same study. Reviewers will not be masked to the articles' authors, institution, or journal.

For all KQ 1-3 applicable studies, reviewers will extract information on general study characteristics (e.g., study design, study period, and follow-up), study participants (e.g., age, sex, race/ethnicity), eligibility criteria as defined in the PICOTS, interventions (e.g., frequency or duration of hemodialysis), outcome measures (see Appendix B for a detailed list of outcomes) and the method of ascertainment, and the results for each outcome including the measure of variability. For studies eligible for abstraction for KQ 4, we will extract the same information on study and participant characteristics as extracted for KQs 1 thru 3. Additionally, we will extract information on psychometric properties, minimally clinically important differences in these instruments, validation, and placebo effect.

Assessment of Methodological Risk of Bias of Individual Studies

KQs 2 and 3

We will assess methodological risk of bias in studies addressing KQs 2 and 3. The assessment of risk of bias will be conducted independently and in duplicate based on the Cochrane Risk of Bias tool for randomized studies,[28] and the Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I).[29] We will supplement these tools with additional assessment questions, such as use of appropriate analysis, based on recommendations in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Methods Guide).[30] We will include observational studies if they have an appropriate comparison group relevant to one of the KQs and adequate long-term follow-up. We will exclude studies if they do not meet a minimal standard for accounting for potential confounders, including a defined control group, and adjustment for differences between groups in baseline renal function/status, risk factors, age, and sex. We may exclude very small observational studies only if larger studies with less risk of bias provide relevant data on each of the outcomes of interest. All study designs must have a follow-up of at least six months. We

will compare the included observational studies to any RCTs. If there is a discrepancy between the observational studies and the RCTs, the overall strength of evidence will be downgraded based on the inconsistency of the evidence. However, we also will comment on the validity of the evidence (noting that RCTs usually provide stronger evidence of validity than observations studies) and the applicability of the evidence to the ESRD Medicare population (which could be a strength of some observational studies). We will follow the AHRQ methods guide on grading the strength of evidence by looking at the strength of evidence for any RCTs, and separately considering the strength of evidence for observational studies. We will consider using sensitivity analysis to assess how conclusions are affected by inclusion versus exclusion of higher risk-of-bias studies.[30]

KQs 1 and 4

We will not evaluate the methodological risk of bias for studies included in KQs 1 or 4 if they do not address KQ 2 or 3.

Data Synthesis

KQs 2 and 3

We will review all primary studies, as defined by our inclusion criteria and KQs, as well as recent meta-analyses. We will perform a de novo meta-analysis including all studies which meet our inclusion criteria when we have sufficient data to do so. We do not anticipate that a comparable meta-analysis or systematic review has been published.

We will only include observational studies that have at least six months of follow-up. RCTs also must have a minimum follow-up of six months. RCTs have been recognized as providing the highest standard of evidence and claims have been made that observational studies may overestimate treatment benefits. RCTs constitute the gold standard for the generation of evidence-based medicine, but may not always be feasible. If we do include data from both RCTs and observational studies, it will not be pooled.[31, 32]

We will address heterogeneity using subgroup analysis and meta-regression if there is sufficient number of studies, or we will describe the heterogeneity qualitatively (see Appendix A for a list of subgroups). We will not combine clinically or methodologically diverse studies. In this situation, we will describe the differences among the studies and population characteristics.

We intend to conduct tests for the presence of statistical heterogeneity, such as Cochran's Q test, as well as a measure of the magnitude of heterogeneity, the I-squared statistic.[28, 30] Interpretation of the Q statistic will consider the limitations of the test that it has low power when the number of studies is small and could detect unimportant heterogeneity when the number of studies is large. In addition, the 95% confidence interval for the I-squared statistic should also be provided, whenever possible, to reflect the uncertainty in the estimate of the magnitude of heterogeneity. Though a naïve categorization of values for I-squared would not be appropriate for all circumstances, we would tentatively assign adjectives of low, moderate, and high to I-squared values of 25%, 50%, and 75%. When statistical heterogeneity is attributable to one or two "outlier" studies, sensitivity analyses

would be conducted by excluding these studies. Sensitivity analysis will be performed when applicable.

KQs 1 and 4

Data collected for these KQs will be qualitatively presented, and we have no plans for quantitative synthesis.

Grading the Strength of Evidence for Major Comparisons and Outcomes

Key Questions 2 and 3

At the completion of this review, two reviewers will independently grade the strength of evidence on comparisons for key outcomes, including QOL, mortality, metabolic and inflammatory control, hypertension and blood pressure control, morbidity, and harms (see Appendix B). In studies including pregnant patients, we will abstract the effect of dialysis dose and/or frequency on pregnancy outcomes. We will use the grading scheme recommended in the Methods Guide.[30] We will consider all domains: study limitations, directness, consistency, precision, reporting bias, dose-response association, plausible confounding that would decrease observed effect, and strength of association (magnitude of effect).[33]

We will classify the evidence pertaining to the KQs into four categories: high grade (high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect); moderate grade (moderate confidence that the evidence reflects the true effect, and further research may change our confidence in the estimate of effect); low grade (low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the effect estimate); and insufficient grade (evidence is unavailable or insufficient to assess with any confidence).

KQs 1 and 4

We do not intend to implement any strategy to grade the strength of the evidence for either of these KQs. KQ 1 addresses collection of data on study and participant characteristics, therefore no analyses will be conducted. KQ 4 is designed to identify and catalogue features of QOL measures used in studies of hemodialysis.

Assessing Applicability

We will consider elements of the PICOTS framework when evaluating the applicability of evidence to answer our KQs as recommended in the Methods Guide.[30] We will consider important population characteristics, treatment characteristics, and settings (Appendix A) that may cause heterogeneity of treatment effects and limit applicability of the findings.

V. References

VI. Definition of Terms

List of acronyms

Acronym	Definition

ABPM	Ambulatory blood pressure monitoring
BP	Blood pressure
CHF	Congestive heart failure
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
ESA	Erythropoiesis stimulating agent
ESRD	End-stage renal disease
FHN	Frequent Hemodialysis Network
KDQOL	Kidney Disease Quality of Life
KQ	Key Question
LV	Left ventricular
MI	Myocardial infarction
PAD	Peripheral artery disease
PICOTS	populations, interventions, comparators, outcomes, timing, setting
QOL	Quality of life
RCT	Randomized controlled trial
SBP	Systolic blood pressure

List of terms

Term	Definition
Dialysis	The process of removing waste products and excess fluid from the body,
End-stage renal disease	End-Stage Renal Disease (ESRD) is a medical condition in which a person's kidneys cease functioning on a permanent basis leading to the need for a regular course of long-term dialysis or a kidney transplant to maintain life.
Hemodialysis	A medical procedure to remove fluid and waste products from the blood and to correct electrolyte imbalances.
Kt/Vurea	The measurement of solute removal during hemodialysis often focuses on urea.

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
June 26, 2019	Methods: Criteria for Inclusion/Exclusion of Studies in the Review	First paragraph: … We will include all studies of the non-institutionalized United States ESRD Medicare population (both adults and children).	First paragraph, additional text: … We will include all studies of the non-institutionalized United States ESRD Medicare population (both adults and children) with the following exceptions: include studies that are conducted in the US and countries outside of the US as long as data are stratified by country; include trials taking place in the US and Canada where the country data are not stratified as long as the majority (51 percent) of study population are in the US.	We are interested in the US ESRD population. There may be studies where the US population is not stratified, but the majority of the patients are from the United States.
June 18, 2019	Initial Publication Date	2019	2018	This was a typo.

VIII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the key questions on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

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

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHSA290201500006I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

XV. References

1. Scribner BH, Cole JJ, Ahmad S, et al. Why thrice weekly dialysis? Hemodial Int. 2004 Apr 1;8(2):188-92. doi: 10.1111/j.1492-7535.2004.01094.x. PMID: 19379416.
2. Toth-Manikowski SM, Shafi T. Hemodialysis Prescription for Incident Patients: Twice Seems Nice, But Is It Incremental? Am J Kidney Dis. 2016 Aug;68(2):180-3. doi: 10.1053/j.ajkd.2016.04.005. PMID: 27477358.
3. 2015 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD: United States Renal Data System; 2015. http://www.usrds.org/adr.aspx. Accessed on October 8, 2018.

4. McCullough KP, Morgenstern H, Saran R, et al. Projecting ESRD Incidence and Prevalence in the United States through 2030. J Am Soc Nephrol. 2019 Jan;30(1):127-35. doi: 10.1681/asn.2018050531. PMID: 30559143.
5. Shafi T, Jaar BG, Plantinga LC, et al. Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. Am J Kidney Dis. 2010 Aug;56(2):348-58. doi: 10.1053/j.ajkd.2010.03.020. PMID: 20605303.
6. Meyer TW, Hostetter TH. Uremia. N Engl J Med. 2007 Sep 27;357(13):1316-25. doi: 10.1056/NEJMra071313. PMID: 17898101.
7. Shafi T, Levey AS. Measurement and Estimation of Residual Kidney Function in Patients on Dialysis. Adv Chronic Kidney Dis. 2018 Jan;25(1):93-104. doi: 10.1053/j.ackd.2017.09.001. PMID: 29499893.
8. Meyer TW, Sirich TL, Fong KD, et al. Kt/Vurea and Nonurea Small Solute Levels in the Hemodialysis Study. J Am Soc Nephrol. 2016 Nov;27(11):3469-78. doi: 10.1681/asn.2015091035. PMID: 27026365.
9. Depner TA. Uremic toxicity: urea and beyond. Semin Dial. 2001 Jul-Aug;14(4):246-51. PMID: 11489197.
10. McAdams-DeMarco MA, Tan J, Salter ML, et al. Frailty and Cognitive Function in Incident Hemodialysis Patients. Clin J Am Soc Nephrol. 2015 Dec 7;10(12):2181-9. doi: 10.2215/cjn.01960215. PMID: 26573615.
11. Bass EB, Wills S, Fink NE, et al. How strong are patients' preferences in choices between dialysis modalities and doses? Am J Kidney Dis. 2004 Oct;44(4):695-705. PMID: 15384021.
12. Kimmel PL, Cohen SD, Weisbord SD. Quality of life in patients with end-stage renal disease treated with hemodialysis: survival is not enough! J Nephrol. 2008 Mar-Apr;21 Suppl 13:S54-8. PMID: 18446733.
13. Ramkumar N, Beddhu S, Eggers P, et al. Patient preferences for in-center intense hemodialysis. Hemodial Int. 2005 Jul;9(3):281-95. doi: 10.1111/j.1492-7535.2005.01143.x. PMID: 16191079.
14. DePasquale N, Ephraim PL, Ameling J, et al. Selecting renal replacement therapies: what do African American and non-African American patients and their families think others should know? A mixed methods study. BMC Nephrol. 2013 Jan 14;14:9. doi: 10.1186/1471-2369-14-9. PMID: 23317336.
15. Hercz G. The Trauma of Dialysis Initiation. J Am Soc Nephrol. 2017 Oct;28(10):2835-7. doi: 10.1681/asn.2017020212. PMID: 28848001.
16. Chertow GM, Levin NW, Beck GJ, et al. In-center hemodialysis six times per week versus three times per week. N Engl J Med. 2010 Dec 9;363(24):2287-300. doi: 10.1056/NEJMoa1001593. PMID: 21091062.
17. Sirich TL, Fong K, Larive B, et al. Limited reduction in uremic solute concentrations with increased dialysis frequency and time in the Frequent Hemodialysis Network Daily Trial. Kidney Int. 2017 May;91(5):1186-92. doi: 10.1016/j.kint.2016.11.002. PMID: 28089366.
18. Vandecasteele SJ, Kurella Tamura M. A patient-centered vision of care for ESRD: dialysis as a bridging treatment or as a final destination? J Am Soc Nephrol. 2014 Aug;25(8):1647-51. doi: 10.1681/asn.2013101082. PMID: 24833125.
19. Churchill DN, Jassal SV. Dialysis: destination or journey. J Am Soc Nephrol. 2014 Aug;25(8):1609-11. doi: 10.1681/asn.2014040390. PMID: 24833126.
20. Williams WW, Delmonico FL. The End of Racial Disparities in Kidney Transplantation? Not So Fast! J Am Soc Nephrol. 2016 Aug;27(8):2224-6. doi: 10.1681/asn.2016010005. PMID: 26952001.
21. Rocco MV, Daugirdas JT, Greene T, et al. Long-term Effects of Frequent Nocturnal Hemodialysis on Mortality: The Frequent Hemodialysis Network (FHN) Nocturnal Trial. Am J Kidney Dis. 2015 Sep;66(3):459-68. doi: 10.1053/j.ajkd.2015.02.331. PMID: 25863828.
22. Rahman M, Griffin V, Kumar A, et al. A comparison of standardized versus "usual" blood pressure measurements in hemodialysis patients. Am J Kidney Dis. 2002 Jun;39(6):1226-30. doi: 10.1053/ajkd.2002.33395. PMID: 12046035.
23. Shafi T, Jaar BG. Maintaining Patients on Home Hemodialysis: The Journey Matters as Does the Destination. Clin J Am Soc Nephrol. 2017 Jul 24. doi: 10.2215/cjn.06890617. PMID: 28739574.
24. Nephrology ASo. Kidney Week. 2019. https://www.asn-online.org/education/kidneyweek/archives/. Accessed on January 18 2019.
25. Foundation NK. 2019 Spring Clinical Meetings. 2019. https://www.kidney.org/spring-clinical/previous-abstracts. Accessed on January 18 2019.

26. University N. Health Measures: Transforming How Health is Measured. 2019. http://www.healthmeasures.net/explore-measurement-systems/promis. Accessed on January 18 2019.
27. AMSTAR. Assessing the Methodological Quality of Systematic REviews. 2017. http://amstar.ca/. Accessed on January 18 2019.
28. Higgins JPT GS, ed Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]; 2011.
29. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. Bmj. 2016 Oct 12;355:i4919. doi: 10.1136/bmj.i4919. PMID: 27733354.
30. Quality AfHRa. AHRQ EHCP Methods Guide for Comparative Effectiveness Reviews of Medical Interventions (Provisional 11-2010). 2010.
31. Castillo RC, Scharfstein DO, MacKenzie EJ. Observational studies in the era of randomized trials: finding the balance. J Bone Joint Surg Am. 2012 Jul 18;94 Suppl 1:112-7. doi: 10.2106/jbjs.l.00242. PMID: 22810460.
32. Shikata S, Nakayama T, Noguchi Y, et al. Comparison of effects in randomized controlled trials with observational studies in digestive surgery. Ann Surg. 2006 Nov;244(5):668-76. doi: 10.1097/01.sla.0000225356.04304.bc. PMID: 17060757.
33. Berkman ND, Lohr KN, Ansari M, et al. AHRQ Methods for Effective Health Care: Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.

Appendix A: List of factors to consider for subgroup analysis

Age
Access to care
Adherence
Cardiovascular disease
Depression
Diabetes
Education
Family support
Gender
Income
Medical literacy
Race/ethnicity
Rural/non-rural
Socioeconomic status
Time on dialysis
Transplant status
Transportation

Appendix B: Main outcomes of interest

Measures
Metabolic/inflammatory control
Phosphorus level
Phosphorus binders
Potassium level
Normalized protein catabolic rate
Albumin level
CRP level
Hemoglobin level
ESA use
Hypertension control pressure control
Clinic SBP (and report how it was measured)
Clinic DBP (and report how it was measured)
ABPM average SBP
ABPM average DBP
Number of BP meds
LV mass
Morbidity
Hospitalization rate
CVD event rate
MI events
Stroke events
CHF events
PAD events
Infection event rate
Vascular Access interventions/thrombosis
Compliance and adherence
Time to recovery from hemodialysis
Quality of life
Sf-36 overall
Sf-36 each component
KDQOL overall
KDQOL each component
Other QOL instruments?
Patient compliance
Patient burden/Caregiver burden
Mortality
Overall mortality rate
CVD mortality rate
Infection mortality rate
Harms of more frequent dialysis
Hypotension
Vascular access complications/thrombosis

Measures
Loss of residual kidney function
Patient and caregiver burden
Pregnancy
Surviving infants
Neonatal deaths
Spontaneous abortions
Birth weight
Preterm delivery
Malformations
Other neonatal complications

ABPM=Ambulatory blood pressure measure; BP=Blood pressure; CHF=Congestive heart failure; CRP=C-reactive protein; CVD=Cardiovascular disease; DBP=Diastolic blood pressure; ESA=Erythropoiesis stimulating agent; KDQOL=Kidney Disease Quality of Life Instrument; LV=Left ventricular; MI=Myocardial infarction; PAD=Peripheral artery disease; SBP=Systolic blood pressure

Appendix C: Detailed preliminary search strategies

PubMed Search for KQs 1 through 3 (last run on 6 December 2018)

1	"Kidney Failure, Chronic"[Mesh]
2	"kidney failure"[tiab]
3	"end stage renal"[tiab]
4	“end stage kidney”[tiab]
5	“chronic renal failure”[tiab]
6	ESRD[tiab]
7	ESKF[tiab]
8	ESKD[tiab]
9	ESRF[tiab]
10	Combine 1 thru 9 with “OR”
11	"Renal Dialysis"[Mesh]
12	hemodialysis[tiab]
13	dialysis[tiab]
14	haemodialysis[tiab]
15	Combine 11 thru 14 with “OR”
16	Frequency[tiab]
17	frequent[tiab]
18	day[tiab]
19	daily[tiab]
20	week[tiab]
21	weekly[tiab]
22	quotidian[tiab]
23	Duration[tiab]
24	nocturnal[tiab]
25	night[tiab]
26	nightly[tiab]
27	overnight[tiab]
28	overnight[tiab]
29	intensive[tiab]
30	extended[tiab]
31	Combine 16 thru 30 with “OR”
32	10 AND 15 AND 31
	Limit to 2005 to present

PubMed search for KQ4 (last run on 6 December 2018)

1	"Kidney Failure, Chronic"[Mesh]
2	"kidney failure"[tiab]
3	"end stage renal"[tiab]
4	“end stage kidney”[tiab]

5	“chronic renal failure”[tiab]
6	ESRD[tiab]
7	ESKF[tiab]
8	ESKD[tiab]
9	ESRF[tiab]
10	Combine 1 thru 9 with “OR”
11	"Quality of Life"[Mesh]
12	"quality of life"[tiab]
13	Combine 11 thru 12 with “OR”
14	10 AND 13
	Limit to “review”