Evidence-based Practice Center Systematic Review Protocol

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

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(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.

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

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

- Intermediate outcomes (see Appendix B for a detailed list of outcomes): metabolic/inflammatory control, blood pressure control, dialysis recovery time

KQ 4:

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]

repository for archiving

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.highe

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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,

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

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

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.

Appendix B: Main outcomes of interest

Measures

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	

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”