Evidence-based Practice Center Technology Assessment Protocol

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

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, 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.[5] 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)

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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)

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

Interventions

- x KQ 1: Different frequency or duration of hemodialysis
  - x KQ 2: More frequent hemodialysis (3 versus 3 > sessions/week)
- x KQ 3: Increased duration of hemodialysis sessions (12 hours versus 12 > hours per week; or daytime versus night time)
- x KQ 4: For this question, we will include studies of QOL in people with ESRD receiving any type of dialysis.
- x 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)

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

Outcomes

- x KQ 1: Not applicable (see Appendix A for a list of the patient characteristics that will be considered for this KQ)
- x KQs 2 and 3:
  - o Final health outcomes (see Appendix B for a detailed list of outcomes): clinical outcomes including cardiovascular events, hospitalizations, QOL, pregnancy outcomes, and mortality
  - o 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
  - o Intermediate outcomes (see Appendix B for a detailed list of outcomes): metabolic/inflammatory control, blood pressure control, dialysis recovery time
- x KQ 4:
  - o Instruments used to measure QOL in dialysis patients
  - o Psychometric properties of these instruments

- Minimal clinically important difference for these instruments

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 conducted in 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 home dialysis or in-center settings.

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

Two comprehensive search strategies will be developed 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 fyl orond wrin the(be215 Td [(0o da)4(7r)5(iv)2((e)4(l)-2(opa3ltTd ([(()B(f)-

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

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 measurev(e)41(evc 0 Tw .242 0 Td ( )Tj -0.004 Tc 0.0

strength of evidence for any RCTs, and separately considering the strength of evidence for observational studies.

Grading the Strength of Evidence forMajor 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 4).

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

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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. [illegible]

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

Effectiveness and Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.

Appendix B: Main outcomes of interest

Measures
Metabolic/inflammatory control
Phosphorus level
Phosphorus binders
Potassium level

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]

5 “chronic renal failure”[tiab]