Evidence-based Practice Center Technical Brief Protocol

Project Title: Renal Denervation in the Medicare Population

Project ID: RENT1115

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I. Background and Objectives for the Technical Brief

Hypertension is the leading cause of cardiovascular disease, kidney failure and death in the general population. In the U.S., the prevalence of hypertension in adults was 29% in 2012.[1] Hypertension prevalence is even higher in the Medicare population, exceeding 60% for adults older than 65 years to over 90% for Medicare dialysis patients.[2, 3] Evidence-based practice guidelines affirm that treatment of hypertension reduces the risks of cardiovascular disease and death, and multiple medications and lifestyle interventions can reduce blood pressure (BP).[4-7]

Despite guidelines supporting BP control, less than half of adults with hypertension reach goal BP, as defined by the older guidelines (less than 140/90 mm Hg).[1] Recently, the landmark Systolic Blood Pressure Intervention Trial (SPRINT) reported that targeting systolic BP of 120 mm Hg instead of 140 mm Hg reduced rates of cardiovascular events by almost a third and the risk of death by almost a quarter.[8] If this lower BP target is adopted by clinicians, an even greater proportion of US adults with hypertension will be above the goal BP, highlighting the importance of new methods for controlling BP.

Failure to reach goal BP despite "adequate" treatment is operationally defined as "Apparent Treatment Resistant Hypertension (aTRH)."[9, 10] The definition was developed to: a) identify patients with secondary causes of hypertension, such as pheochromocytoma, syndrome of apparent mineralocorticoid excess, or renal artery stenosis, that have specific medical or surgical treatments; b) identify patients with uncontrolled BP that may benefit from specialized hypertension care; and c) provide a framework for testing therapies for resistant hypertension. Patients with aTRH can include those with "pseudo-resistance" from dietary, lifestyle, and medication non-adherence and those with "true resistance." Data from 14,684 participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) suggest that irrespective of the mechanism, patients with aTRH are at 30

percent to 50 percent higher risk for death, stroke, or coronary heart disease, and almost 2-fold higher risk of end-stage renal disease compared with patients without aTRH.[11]

In this context, innovative methods to reduce BP, such as renal denervation (RDN), may offer a way to improve cardiovascular outcomes and reduce the risk of myocardial infarction, stroke, kidney failure, disability, and death. Clinical trial data are conflicting about the efficacy of RDN in lowering BP, with resulting uncertainty regarding its role in hypertensive patients. Clarifying the role of RDN in routine care of Medicare beneficiaries requires an understanding of: a) the pathogenesis of hypertension in patients over the age of 65 years, disabled individuals, and those on dialysis; b) factors that contribute to aTRH in these subgroups; c) other options for treatment; and d) a synthesis of the available studies.

II. Guiding Questions

In this section we will map the generic Guiding Questions (GQ) used in technical briefs prepared by the Evidence-based Practice Centers (EPCs) to the specific Key Questions (KQ) that will be addressed in this technical brief. We discuss these in detail below.

GQ 1: Describe the Technology/Intervention

KQ 1. What is the theoretical RDN mechanism of action?

Approach: Narrative review

Discussion: In this section, we will address the generic GQ about describing the RDN technology, and the specific KQ about RDN's mechanism of action. The description of the technology requires an explanation of RDN's mechanism of action, so we will focus on the contribution of renal sympathetic hyperactivity as a contributor to resistant hypertension and how it is affected by RDN. We will discuss possible techniques to differentiate those with hyperactivity versus those without. After explaining the mechanism of action of RDN, we will identify the different RDN devices for which data are available in the public domain, and will compare their technical differences that may affect the completeness of an RDN procedure. A preliminary search yielded a large number of devices, including the following: Symplicity, EnligHTN, OneShot, V2, Paradise, TIVUS, Bullfrog, Surround Sound, Micro-Infusion, Ultrasound, and Radiofrequency. We will review the training and/or certification required to use these devices, who provides the training and carries out the procedure (such as interventional radiology, electrophysiology, interventional cardiology, or vascular surgery), and the methods for maintaining quality control (if any). Finally, we will review the complications of the RDN procedure, differentiating between complications from the vascular access procedure (local pseudoaneurysm, hematoma, blood clot), general renal arterial access complications (cholesterol embolization, dissection, bleeding), and specific complications directly due to the RDN device such as the impact of "burn" on

renal artery and surrounding structures. We will also determine if there are reported or potential systemic consequences of RDN.

GQ 2: Describe the Context in which the Technology/Intervention Is Used

KQ 2. What is the evidence for BP measurement and use as a surrogate outcome?

Approach: Narrative Review

Discussion: For this question, we will summarize evidence from highly regarded authoritative sources and practice guidelines from the American and European professional societies devoted to cardiology and hypertension. We will highlight the rationale for using BP as a surrogate target for reducing the risk of cardiovascular disease in patients with hypertension.

KQ 3. What is the clinical definition of resistant hypertension, and what are the treatment alternatives?

Approach: Narrative review

Discussion: Defining resistant hypertension is key to putting the studies for RDN in context. For this question, we will review the definitions of resistant hypertension proposed by the clinical practice guidelines, and their operationalization in clinical trials of resistant hypertension. The goal will be to summarize these definitions, and develop a framework for assessing studies of RDN. In particular, we will consider the number of medications used to categorize resistant hypertension, the role of lifestyle modifications, assessment of adherence to medications and lifestyle modifications, and the optimal duration of a "run-in" period prior to interventions for resistant hypertension. Finally, we will summarize key features of the studies of resistant hypertension, and list the different treatment alternatives.

KQ 4. For randomized controlled trials (RCTs) and observational studies of RDN, what are the inclusion criteria for patients, and how do clinical characteristics match the clinical definition of resistant hypertension?

Approach: Systematic review of published studies

Discussion: For KQ4, we will use the definition of resistant hypertension and the description of RDN in previous sections to set up the framework for systematically reviewing studies in this section. We anticipate a large degree of heterogeneity in the published literature on RDN. We will review published studies, classifying them as observational (case-control, retrospective/historical controls, or no controls [case series]) and clinical trials (with comparison to sham treatment, placebo, or no additional intervention). We will examine inclusion/exclusion criteria with particular attention to whether the study population matches Medicare beneficiaries (65 years or older, disabled, and dialysis patients). We will compare the inclusion criteria to the definitions of resistant hypertension synthesized from KQ3. We will describe the procedural aspects of the

intervention, including the device used and the training of the operator. Finally, we will abstract the pre-specified endpoints and duration of follow-up in each study.

GQ 3: Describe the Current Evidence of the Technology/Intervention

KQ 5. What are the predictors of response in Medicare eligible patients who are appropriate candidates for RDN?

Approach: Systematic review of published studies

Discussion: We anticipate that most studies will use BP as a surrogate end-point for response (as we will discuss in response to KQ2). We will determine the overall BP response in each study, and review subgroup data to abstract response rates in Medicare eligible sub-groups. We will identify factors associated with response, overall and in subgroups, while making note of differences between studies in the factors associated with response.

KQ 6. What is the evidence for RDN effectiveness in reducing BP, stroke, myocardial infarction, and hospitalization and/or improving survival in Medicare eligible patients with resistant hypertension?

KQ 7. What is the evidence for RDN effectiveness in other conditions such as heart failure and arrhythmias?

Approach: Systematic review of published studies

Discussion: For KQ6 and KQ7, we will abstract each of these listed outcomes if reported in the studies, overall and by subgroups, with particular emphasis on the Medicare eligible population. We will exclude case reports. We will look carefully for data on long-term outcomes.

KQ 8. What are the adverse effects or complications associated with RDN in the Medicare population?

Approach: Systematic review of published studies

Discussion: We will abstract complications reported in the studies, matching them with the potential complications of RDN as outlined in KQ1. We will also assess if the study criteria excluded patients with higher risk of complications. We will explore whether complication rates are associated with device, operator, or the setting.

GQ 4: Identify the Important Issues Raised by the Technology/Intervention

Approach: High-level synthesis/summary of the findings

Discussion: In this section, we will summarize our findings, focusing on efficacy of the RDN procedure, associated risks, and factors that may influence the effectiveness of RDN in real-life clinical practice. We will highlight the areas of uncertainty that remain with the current studies. Finally, we will discuss potential future directions including explanatory/classic or pragmatic trial designs that may be required to generate stronger

evidence about the efficacy and effectiveness of RDN for treatment of resistant hypertension. We will not discuss cost implications as that would require a separate study with careful consideration of the various aspects of healthcare, individual, and societal costs, which are beyond the scope of this project.

III. Methods

1. Data Collection:

A. Discussions with Key Informants

With approval from the Task Order Officer (TOO), we recruited Key Informants. Key Informants included representative stakeholders, including clinical experts, investigators, and patient/consumer advocates. As partners, the Centers for Medicare and Medicaid Services (CMS) representatives were included among our Key Informants. We used a conference call to obtain input from the Key Informants. For the narrative review on KQs 1-3, we asked the Key Informants to verify our interpretation of the prevailing views of experts, and point out any divergent viewpoints that should receive more attention. For the systematic review of evidence on KQs 4-8, we asked the CMS representatives and other Key Informants to provide feedback on our strategy for preparing a summary of the evidence, aiming to perform the work in a systematic yet efficient manner. We also asked them for suggestions regarding for the literature search. The EPC a followed the requirements of the Office of Management and Budget in limiting the number of Key Informants asked the same questions to no more than 9 participants. We submitted a summary of the communication with the Key Informants to the TOO.

B. Grey Literature search.

To find studies in this emerging field, we will search for information about research in progress or not yet published by searching the National Institutes of Health (NIH) Research Portfolio Online Reporting Tools (RePORTER) database and ClinicalTrials.gov, as well as Cochrane Collaboration protocols. We also will look for publicly available information on the Web sites of manufacturers of the relevant technology. We will search the Food and Drug Administration (FDA) Web site for any unpublished additional studies relevant to this topic.

C. Published Literature search.

We will conduct systematic searches for studies addressing KQs 4-8, using PubMed. We also will identify relevant articles from investigators' existing resources, including recommendations by Key Informants and the experts on our team. The search strategy for PubMed is provided in Table 1. We will limit the search to the last 10 years because we do not expect to find any relevant studies

published before 2006. Indeed, the first reported use of the RDN technology in a human being was not published until 2010.[12]

Table 1. PubMed search strategy for renal denervation

Search #	Query	Hits
1	denervation[mh] AND (kidney[mh] OR "renal artery"[mh])	2247
2	"renal denervation"[tiab] OR "renal-artery denervation"[tiab] OR "renal artery denervation"[tiab] OR "renal sympathetic denervation"[tiab]	1796
3	#1 or #2	2941
4	#3 AND (Addresses[ptyp] OR News[ptyp] OR Patient Education Handout[ptyp] OR Bibliography[ptyp] OR Dictionary[ptyp] OR Directory[ptyp] OR Legal Cases[ptyp] OR Legislation[ptyp] OR Newspaper Article[ptyp] OR Periodical Index[ptyp])	7
5	#3 NOT #4	2934
6	#5 NOT (animal[mh] NOT human[mh])	1266
7	#6 AND "2005/01/01"[pdat] : "2015/12/31"/[pdat]	1098

Study eligibility criteria were defined in terms of Population, Intervention, Comparison, Outcomes, Setting, and Timing, and individualized to the questions (Table 2). We will update the search during the peer review process.

Table 2. Inclusion and exclusion criteria for renal denervation studies

	Inclusion	Exclusion
Population	• We will include studies of adults with resistant hypertension (at least 3 medications and blood pressure >140/90 mmHg)	
Intervention	• We will include studies that evaluate a non-surgical renal denervation device	
Comparison	• We will compare studies that compare renal denervation to either anti-hypertensive drugs or lifestyle changes. • We will allow both concurrent comparison groups and before/after comparisons.	
Outcomes	• We will include studies addressing at least one of the following outcomes: o Reduction in hypertension o Morbidity o Mortality o Adverse events o Patient-specific criteria for improved outcomes	
Timing	• We will include studies of any followup duration	
Study design	• We will include randomized controlled trials, comparative observational studies with at least 10 participants per arm, or non-comparative observational studies with less than 25 participants receiving renal denervation. • We will include clinical trials published only as meeting or conference abstracts if the meeting or conference was for a major medical society held within the last 2 years.	• We will exclude case reports. • We will exclude studies with no original data. • We will exclude studies not published in English.

mm Hg = millimeters of mercury

2. Data Organization and Presentation:

A. Information Management

We abstracted data on the items listed in Table 3.

Table 3. Items for data abstraction

Population	• Age and sex • Race/ethnicity • Baseline blood pressure, body mass index, kidney function, diabetes status, left ventricular hypertrophy, and medication use
Intervention	• Manufacturer and model of renal denervation device • Who performed the procedure • Training for procedure • Co-interventions, including a diuretic
Comparator	• Type of comparator, if any • Co-interventions, including a diuretic
Outcomes	• Change in blood pressure, rates of stroke, myocardial infarction, hospitalization, and mortality • Adverse events • Left ventricular hypertrophy • Central aortic stiffness • Ventricular rate in atrial fibrillation • Frequency of ventricular arrhythmia • Symptoms of congestive heart failure
Timing	• Duration of run-in period • Followup duration
Study design	• Study design • Inclusion/exclusion criteria, including the minimum number of antihypertensive medications, the minimum blood pressure, and minimum duration of resistant hypertension. • Number screened versus the number enrolled
Setting	• Geographic location • Setting of renal denervation

B. Data Presentation

We will use a narrative review to answer KQs 1 to 3. We will emphasize the prevailing view on each question, while noting where different points of view exist.

We will use a systematic approach to answer KQs 4 to 8. We will compare how the study eligibility criteria compare to the consensus definition of resistant hypertension given that inclusion criteria in observational studies and RCTs have been variable. We will examine and compare results of the subgroup analyses by age in each of the trials. We also will consider potential effects of RDN on intermediate outcomes, such as left ventricular hypertrophy, and central aortic stiffness, as well as reported effects in reducing the ventricular rate in atrial fibrillation, reducing the frequency of ventricular tachycardia/ventricular fibrillation, and improving symptoms of congestive heart failure. We will summarize any analyses of demographic or clinical characteristics associated with response to RDN. We will address the same issues in trials of RDN that focused on patients with heart failure or arrhythmias. We will summarize and compare the data on adverse effects and complications in each of the trials.

IV. References

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V. Definition of Terms

ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

aTRH = apparent treatment resistant hypertension

BP = blood pressure

CMS = Centers for Medicare and Medicaid Services

EPC = Evidence-based Practice Center

FDA = Food and Drug Administration

GQ = Guiding Question

KQ = Key Question

NHLBI = National Heart, Lung, and Blood Institute

NIH = National Institutes of Health

RCT = randomized controlled trial

RDN = renal denervation

RePORTER = Research Portfolio Online Reporting Tools

SPRINT = Systolic Blood Pressure Intervention Trial

TOO = Task Order Officer

VI. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

(NOTE THE FOLLOWING PROTOCOL ELEMENTS ARE STANDARD SECTIONS TO BE ADDED TO ALL TECHNICAL BRIEF PROTOCOLS)

VII. Key Informants

Within the Technical Brief process, Key Informants serve as a resource to offer insight into the clinical context of the technology/intervention, how it works, how it is currently used or might be used, and which features may be important from a patient of policy standpoint. They may include clinical experts, patients, manufacturers, researchers, payers, or other perspectives, depending on the technology/intervention in question. Differing viewpoints are expected, and all statements are crosschecked against available literature and statements from other Key Informants. Information gained from Key Informant interviews is identified as such in the report. Key Informants do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

VIII. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

IX. 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.

X. Role of the Funder

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