Research Review Disposition of Comments Report

July 2016

Research Review Title: *Renal Denervation in the Medicare Population*

Draft review available for public comment from March 3, 2016 to March 31, 2016.

Research Review Citation: Shafi T, Chacko M, Berger Z, Wilson LM, Gayleard J, Bass EB, Sozio SM. Renal Denervation in the Medicare Population. Technology Assessment Program Project ID: RENT1115.(Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2015-00006-I) Rockville, MD: Agency for Healthcare Research and Quality; July 2016. Available at: http://www.ahrq.gov/research/findings/ta/index.html

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site or AHRQ Web site in draft form for public comment for a 3-4-week period. Comments can be submitted via the Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	The report presents a balanced assessment of the relevant literature and highlights the imperative off using ABPM as the metric by which beneficial reduction of blood pressure is determined.	Thank you for reviewing our report!
Peer Reviewer #1	General	The report might give more attention to the methodology of renal denervation, such as the catheter used, the artery (or arteries) selected, and the site of denervation (proximal or distal).	Thank you for this comment. We added information regarding the type of catheter used to Table 7. Most studies did not specify the site of denervation.
Peer Reviewer #1	General	The expertise required and the complexity of investigations to exclude secondary hypertension might be emphasized.	We agree with the comment and have re-emphasized the importance of thorough evaluation of secondary hypertension in the Discussion Section.
Peer Reviewer #1	General	Finally, the recent Pathway studies showing that resistant hypertension is something of a rarity if spironolactone is added to medication, might be mentioned.	We added this information to KQ3 where we describe the PATHWAY-2 Trial.
Peer Reviewer #1	Introduction	Introduction is reasonable but might consider the above comments.	We discuss secondary causes of resistant hypertension in the Introduction.
Peer Reviewer #1	Methods	I think the methodology is very sound.	Thank you for reviewing our report!
Peer Reviewer #1	Results	I would regard the results section as being adequate.	Thank you for reviewing our report!
Peer Reviewer #1	Discussion/ Conclusion	This is adequate in my opinion. As to how the recommendations will be taken into account is debatable. The UK moratorium on the use of renal denervation might be given consideration. See The Joint UK Societies' Consensus Statement on Renal Denervation for Resistant Hypertension. 2016	Thank you for the comment. We have added reference to the Joint UK Societies' 2014 Consensus Statement to the Future Research Needs section of the discussion. While some of the same studies are highlighted in that report, our systematic review of this topic will inform key stakeholders of the available literature and its limitations for the US Medicare population. In the Discussion section for this report, we focus on the findings from our study and the implications of these findings.
Peer Reviewer #1	Clarity and Usability	Overall the report highlights the past difficulties with the technique and indicates the research that is needed before it can become relevant to clinical practice..	Thank you for the comment.
Key Informant #1	General	This is a thoroughly crafted and meaningful report. It has included all the appropriate studies and has tackled the key questions in a thoughtful manner.	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
Key Informant #3	Introduction	Page 1, Line 42-43: Add "heart failure" to read: "…kidney failure, heart failure, disability, and death." Is there a reason to believe that the innovative methods would have results inconsistent with the results of SHEP (Kostis et al. JAMA 1997), ALLHAT (see refs in Einhorn et al. Current Opinion in Cardiology 2010), HYVET (Beckett et al. NEJM 2008), and SPRINT (NEJM 2015) regarding prevention of heart failure?	We have added "heart failure" to the list in the fourth paragraph of the Introduction.
Key Informant #3	Methods	The inclusion/exclusion criteria are justifiable. The search strategies are explicitly stated and logical. I have a minor suggestion for clarification in Table 2, P. 4, Line 45: "Whether up-titration of medications was allowed?"	We have edited this bullet in Table 2 to read, "Whether up-titration of antihypertensive medications was allowed."
Key Informant #3	Results	The results section is well-written, with an appropriate level of detail.	Thank you for reviewing our report!
Key Informant #3	Results	Page 7, Line 34: It may be too early for head-head-studies	Thank you for the comment. We are simply noting here that there are no head-to-head studies.
Key Informant #3	Results	Page 8, Line 18: Suggest adding "heart failure" to the benefits of lowering BP, especially given the SPRINT trial results. Refs to add: Kostis et al. JAMA 1997 (SHEP), select from refs Einhorn et al. Current Opinion in Cardiology 2010 (ALLHAT), Beckett et al. NEJM 2008 (HYVET), and NEJM 2015 (SPRINT). Please note the benefit for preventing heart failure is greater than for the other outcomes.	We have added "heart failure" to the list in the second paragraph under KQ2. We have also added in the references.
Key Informant #3	Results	Page 9, Line 5: Maybe add main ALLHAT results papers to ref. 11 (JAMA 2002, Hypertension 2003)?	We added these references to the third paragraph under KQ2.
Key Informant #3	Results	Page 11, Line 20: In Table 5, BMI is identical across types of studies. Is there a typo in the table?	Under the "Other Inclusion Criteria and Clinical Characteristics of the Patients" section of KQ4, we have edited the sentence to read, "Compared with non-randomized trials, the RCTs were characterized by a larger sample size, a lower prevalence of diabetes, and a mean estimated glomerular filtration rate that was higher than that found in the non-randomized trials."
Key Informant #3	Results	Page 11, Line 20-21: Suggest to use eGFR instead of	We have changed the sentence to include

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		CKD changes. CKD changes seem difficult to interpret in Table 5.	estimated glomerular filtration rate instead of chronic kidney disease stages.
Key Informant #3	Results	Page 13, Line 57: Should it be Table 5 (not 3)?	Yes, you are correct. We have made this change.
Key Informant #3	Results	Page 15, Line 17: Suggest adding size of the study (N=) to the first column in Table 6. Were the analyses of the predictors adjusted? Consider including a comment in the text and more detail in the table footnote, if appropriate.	We added the sample sizes into Table 6. The table uses footnotes to indicate the predictors that were significant in multivariate analysis vs. univariate analysis.
Key Informant #3	Results	Page 17, Line 55: I found the sentence starting with "studies have supported (or reported)…" somewhat difficult to read.	We have changed this sentence to read, "Studies have supported ambulatory measurements as more predictive than office measurements…"
Key Informant #3	Results	Page 20, Figure 2: Is there a reason for the studies reporting office BP measurements not to be tabulated in the main paper while those reporting the ambulatory BP are?	Studies reporting office blood pressure measurements are presented in Table 11. We added a footnote to Figure 2 referring readers to each table.
Key Informant #3	Results	Page 21, Line 9-20: These 2 paragraphs appear to describe the outcome of the overall ambulatory BP versus daytime and nighttime, and thus would fit better under the heading of the 24-hour ambulatory SBP on page 18.	We have moved these two paragraphs, and the corresponding table and figure, to be under the "24-Hour Ambulatory Systolic Blood Pressure" heading.
Key Informant #3	Results	Page 21, Line 19: While the conclusion about a correlation between the highest baseline ambulatory SBP and the changes in SBP is carefully worded, I don't really see it in Figure 3.	We have modified the description in text to "Figure 3 plots the change in ambulatory systolic blood pressure 6 months after renal denervation. The change in systolic blood pressure after denervation varied among the studies."
Key Informant #3	Results	Page 30: A statistician should weigh in regarding reporting these analyses, given the numbers of events.	None of the studies analyzed clinical events as a primary outcome. In this section of the report, we summarize the absolute risk differences. Due to the highly variable nature of the studies, we are not pooling the estimates across studies. We have also added the formula used for calculation of the 95% confidence interval of the risk difference to the footnote of Table 13.
Key Informant #3	Discussion/ Conclusion	The discussion is well-written, including the section on the future research needs. A few specific comments:	Thank you for your careful review of our report. We address each of your comments below.
Key Informant #3	Discussion/	Table 24 is not mentioned in the text.	We added the following to the discussion "This

Commentator & Affiliation	Section	Comment	Response
	Conclusion		is the most comprehensive review of this topic (Table 24)."
Key Informant #3	Discussion/ Conclusion	Page 44, Line 6: I would remove "some" to read "for clinical outcomes;"	We have removed the word "some" from the first sentence under Limitations of the Evidence.
Key Informant #3	Discussion/ Conclusion	Page 45, Line 16: Recommend adding heart failure - as previously explained.	We have added "heart failure" to the Conclusions and Implications.
Key Informant #3	Clarity and Usability	The report is generally well-structured and organized. Minor suggestions were provided in the previous sections.	Thank you for reviewing our report!
Key Informant #3	Clarity and Usability	This technology is in early stage of development with respect to human studies and is not ready for implementation in practice without further research.	We have edited our conclusion and hope it captures this concept.
Public Reviewer St. Jude Medical	General	Dear Madam/Sir: St. Jude Medical appreciated the opportunity to comment on the Agency for Healthcare Research and Quality's (AHRQ) draft report for Renal Denervation in the Medicare Population. St. Jude Medical develops medical technology and services which focus on placing more control in the hands of those who treat cardiac, neurological and chronic pain patients worldwide. The company is dedicated to advancing the practice of medicine by reducing risk wherever possible and contributing to successful outcomes for every patient.	Thank you for reviewing our report!
Public Reviewer St. Jude Medical	Introduction/ Background	The introduction section of the assessment references results of the SPRINT trial indicating systolic blood pressure of 120 mm HG, instead of 140 mmHg, reduces rates of cardiovascular events by almost a third and the risk of death by almost a quarter. However, there was no mention of the significantly higher serious adverse event rates (hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure) in the group with the target systolic blood pressure of 120 mmHg. We recommend the introduction section include information regarding the serious adverse event rates of the SPRINT trial, as this strengthens the argument that currently available pharmaceutical options are not meeting the clinical needs of the patient.	Thank you for the comment. We refer to the SPRINT Trial in the Introduction to highlight that its findings may lead to changes in blood pressure goals and that lower blood pressure goals may translate to a greater proportion of the US population with uncontrolled hypertension. We do not want to speculate or imply that the adverse events from a lower blood pressure target will be different with medications versus other investigational strategies. This hypothesis needs further investigation. In the Future Research Needs section, we added that future trials should investigate the unintended consequences of blood pressure lowering.
Public Reviewer St.	Results	KQ 1. What is the theoretical renal denervation	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
Jude Medical		mechanism of action? We agree with the assessment.	
Public Reviewer St. Jude Medical	Results	KQ2: What is the evidence for blood pressure measurement and use as a surrogate outcome? We agree with the assessment.	Thank you for reviewing our report!
Public Reviewer St. Jude Medical	Results	KQ3: What is the clinical definition of resistant hypertension, and what are the treatment alternatives? We agree with the definition of resistant hypertension; however, the discussion of treatment options is limited. To make this a more complete list of alternatives, we recommend adding alternative surgical and device options, such as cartoid sinus stimulation or sympathectomy.	The goal of KQ3 is to provide a narrative review of current clinical options for resistant hypertension. This section is not intended to be a review of all potential treatment strategies. However, we now recognize in that section that other treatment options are needed.
Public Reviewer St. Jude Medical	Results	KQ4: For randomized controlled trials and observational studies of renal denervation, what are the inclusion criteria for patients, and how do clinical characteristics match the clinical definition of resistant hypertension? In Table 3, there is no mention of the method of blood pressure assessment. There can be a significant different between office and ambulatory pressures due to white coat effect and observer bias. An ambulatory systolic blood pressure of 140 mmHg is likely to be associated with a greater risk for adverse events than the same value via office blood pressure. We recommend the table be updated to reflect the method of blood pressure assessment reported in the various studies.	We report the method of blood pressure measurement with the results (See Tables 7-11 for detailed results of ambulatory and office blood pressure)
Public Reviewer St. Jude Medical	Results	KQ4: Moreover, due to the broadly acknowledged blood pressure sensitivity to environmental and emotional influences, the difference in blood pressure reduction between groups observed in a double-blind, randomized, sham-controlled trial is much more difficult to achieve than in an open label, non-placebo controlled trial. Even a seemingly modest 24-hour systolic ambulatory blood pressure reduction of 1-3 mmHg achieved in such rigorous trials is expected to confer meaningful clinical benefits.	We report the achieved blood pressure differences and ranges in Tables 7-11 and accompanying text for KQ5.
Public Reviewer St. Jude Medical	Results	KQ5: What are the predictors of response in Medicare eligible patients who are appropriate candidates for	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
		renal denervation? We agree with the assessment.	
Public Reviewer St. Jude Medical	Results	KQ6: We agree patients with uncontrolled secondary causes of hypertension should be excluded. If the secondary cause is treated and controlled and the patient remains hypertensive due to underlying essential hypertension, we believe such patients should be included. Therefore, we recommend adding the qualifier "uncontrolled" to the exclusion criteria on secondary hypertension.	Determining whether a secondary cause of hypertension is treated and controlled is difficult enough in clinical care, let along in the setting of research studies. We thank the reviewer for this comment, but feel it is beyond the scope of this systematic review.
Public Reviewer St. Jude Medical	Results	KQ6: While we agree non-adherence to medication should be an exclusion criterion, we disagree lack of adherence to a low salt diet should be tracked and should exclude a patient, for the following reasons: o Adherence to diet is difficult to reliably track, especially in a larger trial. o Very high dietary salt intake has been shown to have heterogeneous responses in persons with salt sensitivity and hypertension (Luft F and Weinberger M, Am J Clin Nutr 1997) due to age, intake of other electrolytes, medication and genomics. o These are not required for anti-hypertensive medication trials. o These requirements would create an artificial environment which would not provide real world conditions to test the effectiveness of the renal denervation therapy. o Patients would have already failed lifestyle modifications by the time they start a medication regimen for their hypertension based on standard of care. This would especially be the case before starting an antihypertensive regimen consisting of three medications or more. o These requirements are not necessary since the randomization would protect against confounding variables, such as lifestyle factors, including diet adherence.	Lifestyle interventions are the first-line therapy for treatment of essential and resistant hypertension recommended by every major guideline. Even though these lifestyle factors are often ineffective in resistant hypertension, we feel it is important to recognize these factors in the design and interpretation of studies on any antihypertensive therapy.
Public Reviewer St. Jude Medical	Results	KQ6: There was no mention of controls over medication regimen after baseline. Changes to the medication regimen during the trial can have a	Thank you for the comment. We describe the ideal study as one that "3) the study will include a sufficiently long run-in period to reduce

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		profound impact on outcomes and potentially mask effects of the renal denervation procedure. We recommend standardizing the medication regimen during the trial and including restrictions on medication changes, at least during the primary endpoint assessment period.	regression to the mean and ensure compliance; and 6) the study will continue to evaluate dietary and medication adherence during followup." As a clinician (or study physician) may change medications as a result of blood pressure changes, we include medication changes as one of our outcomes.
Public Reviewer St. Jude Medical	Results	KQ6: We agree with the rest of the study characteristics.	Thank you for reviewing our report!
Public Reviewer St. Jude Medical	Results	KQ7: What is the evidence for renal denervation effectiveness in other conditions such as heart failure and arrhythmias? We have no comments.	Thank you for reviewing our report!
Public Reviewer St. Jude Medical	Results	KQ8: What are the adverse effects or complications associated with renal denervation in the Medicare population? We agree with the assessment.	Thank you for reviewing our report!
Public Reviewer St. Jude Medical	Results	Future Research Needs: We agree with the assessment.	Thank you for reviewing our report!
Public Reviewer Ablative Solutions, Inc.	Discussion/ Conclusion	The Draft Technical Brief Technology Assessment Report on Renal Denervation in the Medicare Population is an excellent summary of the published research in the field of renal denervation. Unfortunately, the conclusions are skewed by a single, randomized trial using first generation RF technology, which has substantial flaws and limitations. The report does not adequately acknowledge the early state of the understanding of the disease pathophysiology, and the lessons learned since the publication of this negative trial. Ablative Solutions, Inc. wishes to acknowledge these findings. However, we believe that the conclusions should be placed into context, and that there should be strong support for ongoing and future evaluation of emerging, next generation technology, that offer promise for the field of renal denervation.	Our report provides a systematic review of the evidence available to date on using renal denervation in patients with resistant hypertension. We agree that there are many unanswered questions and unmet needs for patients with hypertension. We have revised our Conclusions and Implications section to reflect the need for ongoing research in this area.
Public Reviewer Ablative Solutions, Inc.	Discussion/ Conclusion	Of the 76 trials analyzed from 88 articles, 9 were randomized controlled trials (RCTs). Appropriately, the data from these trials were most heavily weighted in considering the report's overall findings and in drawing conclusions. Of the 7,022 patients studied,	The goal of our report is to summarize the evidence available to-date. We are aware of many commentaries and opinions published after the Symplicity HTN-3 trial. However, our report focuses on systematically reviewing and

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		1,030 came from RCTs. Of these, 535 were from the Symplicity HTN-3 trial, which failed to show a significant treatment effect of blood pressure reduction, with a 14.1mmHg drop in Office Blood Pressure (OBP) in the treatment group, compared to 11.7 mmHg in the control arm, and a decrease of 6.8 mmHg in 24 hr ABPM in the treatment group compared to 4.8 mmHg in the control group.1 Aggregate data from this compilation is heavily skewed by the negative finding in this single large trial, and importantly, lessons learned from this trial are not being applied to the conclusions of this briefing.	presenting the overall level of evidence rather than focus on the shortcomings or positive results from single studies. Due to the marked heterogeneity of the published studies, we did not pool our data and do not believe that our findings are "skewed" by one single study. We now report on future technologic advances in our Discussion section.
Public Reviewer Ablative Solutions, Inc.	Discussion/ Conclusion	In particular, the review fails to cite some very important limitations that suggest that the Symplicity HTN-3 trial, as executed, would have virtually no chance of creating significant renal denervation or having a detectable therapeutic effect. First, the device studied is complex to operate, and operators in the trial had no training in renal denervation. There were no run-in cases to allow the physicians to learn how to use the device properly. There were an average of only 1.8 cases performed per operator, which is clearly inadequate, and allowed inexperienced and untrained physicians to perform the majority of the procedures. Even in experienced hands the device is challenging to use in the prescribed fashion, requiring at least four ablations per artery in each of four quadrants (superior, inferior, anterior, posterior), and maintenance of excellent electrode contact with the vessel wall. As a result of these numerous device and training issues, only a very small fraction of patients received either an adequate number of ablations, and/or ablations in all four quadrants. In fact, there was a mean of only 3.8 ablations/renal artery, which is less than the minimum of four/artery prescribed in the protocol, and less than 25% received ablations in all four quadrants.2 These data are further confounded by major protocol	The goal of our report is to summarize the available evidence on renal denervation at this point and not focus on a single study. We have added additional portions about technologic advances in our Discussion section.

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		violations and inconsistencies related to both escalation of medication compliance and the addition of anti-hypertensive medication during follow-up in both the treatment and the control group (in~40% of the subjects).	
Public Reviewer Ablative Solutions, Inc.	Discussion/ Conclusion	In the aftermath of this trial, much analysis has been done and a great deal learned about the nature of sympathetic innervation of the kidneys, the pathophysiology of denervation, and inherent limitations of different types of technology as well as alternative therapeutic approaches to accomplish denervation. It is now better understood that the sympathetic nerves are distributed farther from the arterial wall at the ostium of the renal artery, and closer more distally. The nerves are located in the adventitia and at a depth of between 1-12 mm, as measured from the intima.3 Successful denervation must provide for an adequate depth of ablation, and circumferential ablation (360o circumference). Radiofrequency (RF) catheters are now known to penetrate only 2-4 mm in depth, thus missing a large number of nerve fibers located deeper in the adventitia, especially when one performs ablation in the proximal portion of the renal artery. A number of pathology publications, and an autopsy report in a human RF case, suggest that there is a very modest depth of ablation (~2 mm) and arc of ablation (~35 degrees/burn) with RF in general and with the Symplicity catheter, as was used in this pivotal trial, in particular, such that the mean sympathetic nerve ablation would be estimated to be 10-20% of the nerve fibers.4 Edelman?s work suggests a threshold minimum of 50% nerve ablation to achieve a physiologic effect.	We acknowledge and agree that complex technical and anatomic issues may play a role in achieving more complete denervation and improving the efficacy of renal denervation and that a better understanding of these issues is important. We have added additional wording about technologic advances in our Discussion section.
Public Reviewer Ablative Solutions, Inc.	Discussion/ Conclusion	Furthermore, the review has ignored a very powerful post hoc analysis of the trial which strongly support the conclusion that inadequate denervation was the root cause of the trial?s failure. In the publication by Kandzari et al.2, one can see a very powerful dose-	We summarize the evidence available to date on renal denervation. Detailed analysis of a single trial is not the focus of this report. We have added a section to the Discussion highlighting the limitations of current methods

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		response in BP lowering as a function of the number of ablations performed per patient. In patients with eight ablations/patient (slightly greater than the trial mean of 7.6) there was only a 13 mmHg office drop in BP and a 4 mmHg drop in ABPM, and no difference vs. control group. However, when one doubles that to >16 ablations per patient the BP reduction was dramatically improved, with a 30 mmHg OBP drop and a 21 mmHg ABPM drop. The full dose-response of ablations vs. BP drop is quite striking, and support the conclusion that the Symplicity HTN-3 trial was highly flawed, and should not be interpreted as a failure of renal denervation, but primarily as a failure to denervate.	for renal denervation and potential for future renal denervation technology.
Public Reviewer Ablative Solutions, Inc.	Discussion/ Conclusion	As evidenced above, all RF catheters have this inherent limitation of limited depth of energy penetration, and so current trials are targeting more distal in the renal arteries, and ablation into the branches, as well as a substantially greater number of thermal ablations than were performed in the Symplicity HTN-3 trial. Recent work by Medtronic has suggested that the only feasible way to get adequate denervation with RF is to perform at least 12 ablations/artery (24 ablations per patient) and to perform these ablations in the distal main renal artery and in the upper and lower distal branch vessels. This is the basis of the ongoing Spyral trial,5 sponsored by Medtronic . Unfortunately, it is possible that this will increase the risk of energy induced injury to the arterial wall, resulting in renal artery stenosis and other complications. Thus, the challenges facing RF approaches to achieve both safe and effective denervation are formidable, but one may be hopeful that at least with adequate denervation we will observe a more powerful signal for BP lowering efficacy.	We acknowledge and agree that complex technical and anatomic issues may play a role in achieving more complete denervation and improving the efficacy of renal denervation and that a better understanding of these issues is important. We have added additional wording about technologic advances in our Discussion section.
Public Reviewer Ablative Solutions, Inc.	Discussion/ Conclusion	The Ablative Solutions Peregrine Catheter is a combination product, currently 510k cleared in the US, and CE marked in Europe. Plans are underway to	We acknowledge and agree that a deeper understanding of the technical and anatomic issues involved in renal denervation may play a

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		begin IND trials in the US using this device with the infusion of ethanol alcohol to perform ?chemical? renal denervation for the treatment of hypertension. This device accomplishes nerve ablation by the infusion/injection of alcohol 3.5 mm deep to the intima and directly into the adventitial space where the nerves reside, and minimizing or eliminating injury to the media. The alcohol diffuses circumferentially and ~ 1-1.5 cm axially, creating denervation equivalent to surgical denervation in animal studies. Procedural variability, and operator experience, important factors in the failure of HTN-3, are minimized by inherent advantages of the Peregrine catheter. In feasibility trials the Peregrine catheter has demonstrated a large treatment effect in lowering BP, which will be further studied in randomized, sham controlled studies.	role in achieving more complete denervation and improving the efficacy of the procedure. Early studies of the Medtronic Symplicity® catheter also demonstrated large treatment effects in lowering blood pressure that were not borne out in the large randomized sham-controlled study, Symplicity HTN-3. Further randomized sham-controlled trials of the Ablative Solutions Peregrine® catheter may be helpful in validating the mechanism of renal nerve ablation if the results of the early clinical trials can be replicated.
Public Reviewer Ablative Solutions, Inc.	Discussion/ Conclusion	In conclusion, much has been learned since the failure of HTN-3 about the pathophysiology of renal denervation, inherent anatomic, technical and procedural variables that must be accounted for in device design, and procedural/trial execution. We have also recognized the importance of proper patient selection and monitoring during properly executed clinical trials. The results as characterized in the AHRQ briefing well characterize the findings to date, but do not place them into proper perspective. The field is young, and trials are ongoing that hopefully validate the treatment modality in general. In addition, all technology is not equivalent. The results of trials must be considered, taking into account the strengths and limitations of each technology as well as the trial conditions, patient inclusion criteria, etc. While we believe that Ablative Solutions has an excellent technology with many inherent benefits, the entire field should be evaluated with a depth of understanding and with the proper perspective. One highly flawed trial that has failed should not be overly relied upon in drawing conclusions about the space, in general. Our recommendation is to acknowledge the	While we agree that the field of renal denervation is in its infancy and that further research with next generation technology and alternative modalities of renal denervation should not be abandoned, a detailed discussion of this is beyond the scope of this systematic review designed to summarize the current level of evidence in the field. We feel that the implications of the trials we summarize are clear and that the case for future research is made.

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		early stage of the research, and reserve full judgment until further ongoing studies are completed.	
Public Reviewer Medtronic PLC	General	Overall, Medtronic is supportive of the methodology and results of the Technical Brief addressing Renal Denervation in the Medicare Population. The conclusions and recommendations are aligned with Medtronic's SPYRAL HTN Global Clinical Trial Program (1) designed to address the limitations of prior studies and provide insight into the impact of pharmacotherapy on renal denervation efficacy. The comments below serve only to address some of the inaccuracies identified in the Brief, but do not reflect a disagreement with the conclusions.	Thank you for reviewing our report!
Public Reviewer Medtronic PLC	Tables	Table 7: Desch, 2015 (ref #77): Table 1 in the Desch paper does report the mean baseline 24-hour systolic ABPM in the RDN group as 140+4.6 and in the control group as 140+5.6 mmHg. However, "NR" is listed in the table.	Thank you. We have added in the baseline 24-hour ambulatory blood pressure for the Desch 2015 study into Table 7.
Public Reviewer Medtronic PLC	Tables	Table 7: Rosa, 2015 (ref #58): The control group box specifies "continuation of anti-hypertensive drugs." However, the so called "control" group in this trial actually had an increase in drugs as most subjects had spironolactone introduced by trial design. By contrast, spironolactone was not introduced in the RDN group as well. Therefore, this is not a controlled study in the same sense as the others listed (e.g. SYMPLICITY HTN 2 SYMPLICITY HTN 3, Desch, DENER HTN) which were true RCTs, since the only variable was RDN therapy in those trials.	In Table 7, we changed the control group for Rosa 2015 to read "Intensification of anti-hypertensive drugs."
Public Reviewer Medtronic PLC	Tables	Table 7: Tsioufis, 2015 (ref #80): No "sham" procedure was actually performed. The control group was not prospective.	In Table 7, we changed the control group for Tsioufis 2015 to read "No renal denervation."
Public Reviewer Medtronic PLC	Tables	Table 8: Desch, 2015 (ref #77): Table 1 in the Desch paper does report the mean day-tome systolic ABPM in the RDN group as 144+4.8 and in the control group as 143+4.7 mmHg. However, "NR" is listed in the table.	Thank you. We have added in the baseline daytime ambulatory blood pressure for the Desch 2015 study into Table 9 (formerly Table 8).
Public Reviewer Medtronic PLC	Tables	Table 8: Rosa, 2015 (ref #58): The control group box specifies "continuation of anti-hypertensive drugs."	In Table 9 (formerly Table 8), we changed the control group for Rosa 2015 to read

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		However, the so called "control" group in this trial actually had an increase in drugs as most subjects had spironolactone introduced by trial design. By contrast, spironolactone was not introduced in the RDN group as well. Therefore, this is not a controlled study in the same sense as the others listed (e.g. SYMPLICITY HTN 2, SYMPLICITY HTN 3, Desch, DENER HTN) which were true RCTs, since the only cariable was RDN therapy in those trials.	"Intensification of anti-hypertensive drugs."
Public Reviewer Medtronic PLC	Tables	Table 8: Azizi, 2015 (ref #56): Instrad of describing Control Group as "continuation of anti-hypertensive drugs" a more accurate statement would be "drugs were increased evenly in both arms."	In Table 9 (formerly Table 8), we describe both arms as having "intensification of anti-hypertensive drugs."
Public Reviewer Medtronic PLC	Tables	Table 9: Desch, 2015 (#77): Table 1 in the Desch paper does report the night-time systolic ABPM in the RDN group as 130.5+9.7 and in the control group as 132.3+11.7 mmHg. The reference to the entire study is not included in the table.	Thank you. We have added in the baseline daytime ambulatory blood pressure for the Desch 2015 study into Table 10 (formerly Table 9).
Public Reviewer Medtronic PLC	Tables	Table 9: Rosa, 2015 (ref #58): The control group box specifies "continuation of antihypertensive drugs." However, the so called "control" group in this trial actually had an increase in drugs as most subjects had spironolactone introduced by trial design. By contrast, spironolactone was not introduced in the RDN group as well. Therefore, this is not a controlled study in the same sense as the others listed (e.g. SYMPLICITy HTN 2, SYMPLICITY HTN 3, Desch, DENER HTN) which were RCTs, since the only variable was RDN therapy in those trials.	In Table 10 (formerly Table 9), we changed the control group for Rosa 2015 to read "Intensification of anti-hypertensive drugs."
Public Reviewer Medtronic PLC	Tables	Table 9: Azizi, 2015 (ref #56): Instead of describing Control Group as "continuation of antihypertensive drugs," a more accurate statement would be "drugs were increased evenly in both arms."	In Table 10 (formerly Table 9), we describe both arms as having "intensification of anti-hypertensive drugs."
Public Reviewer Medtronic PLC	Tables	Table 12: Azizi, 2015 (# 56): Instead of describing Control Group as "continuation of antihypertensive drugs," a more accurate statement would be "drugs were increased evenly in both arms."	In Table 12, we describe both arms as having "intensification of anti-hypertensive drugs."
Public Reviewer Medtronic PLC	Tables	Table 12: Rosa, 2015 (ref #58): The control group box specifies "continuation of antihypertensive drugs."	In Table 12, we changed the control group for Rosa 2015 to read "Intensification of anti-

Commentator & Affiliation	Section	Comment	Response
		However, the so called "control" group in this trial actually had an increase in drugs as most subjects had spironolactone introduced by trial design. By contrast, spironolactone was not introduced in the RDN group as well. Therefore, this is not a controlled study in the same sense as the others listed (e.g. SYMPLICITy HTN 2, SYMPLICITY HTN 3, Desch, DENER HTN) which were RCTs, since the only variable was RDN therapy in those trials.	hypertensive drugs."
Public Reviewer Medtronic PLC	Figures	Figure 2: Azizi, 2015 (ref #56): DENER HTN recorded ambulatory BPM, and therefore should be included under ambulatory section.	Thank you for mentioning this. We have added the ambulatory blood pressure data from Azizi 2015 to the figure.
Public Reviewer Medtronic PLC	Figures	Figure 3: The data in figure 3 does not support the observation that the highest ambulatory systolic blood pressure often represented the greatest change in ambulatory systolic blood pressure after renal denervation. Note the variation in the systolic blood pressure changes across multiple studies. If the baseline pressure is plotted as a function of change in pressure, there is no clear relationship across studies.	We agree and have modified our interpretation of the data presented in the figure.