National Institute for Health and Care Excellence

IP923/2 Percutaneous transluminal renal sympathetic denervation for resistant hypertension

IPAC date: 8th December 2022

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1.	Consultee 1 NHS professional	1.1	The evidence on the efficacy of renal denervation for lowering blood pressure is not limited in quality. Far from it. It is one of, if not the only device in cardiovascular medicine with six positive sham-controlled trials of efficacy for its intended aim – blood pressure lowering. These contemporary trials have been designed with modern devices, modern techniques and using trial designs that are much more robust than the early generation of technologies and trials. Just like with mechanical thrombectomy for stroke, the trials showed uncertain efficacy in the early days until the technology, techniques, patient selection and clinical trial design was perfected. Since RDN did that, we have shown blood pressure lowering efficacy with: RADIANCE SOLO, RADIANCE TRIO, RADIANCE II SPYRAL OFF MED pilot, SPYRAL OFF MED pivotal, SPYRAL ON MED pilot The distinction made by NICE in this IPG is surrounding 'resistant hypertension' a technically correct but now largely outdated concept for many specialists in the field now we have drug adherence measurement techniques, as the significant majority of people with apparent drug resistance actually have intolerance or non-adherence to medications instead. We therefore use the term uncontrolled hypertension, to emphasise that there are many reasons for lack of control. The clinical trials described above and the thousands of patients enrolled in prospective clinical registries such as the GLOBAL simplicity registry represent about as robust a base as it is possible to get. The only distinction made in this consultation is the term 'resistant hypertension', meaning BP >140/90 despite three meds including a diuretic. There are millions of patients in the UK with uncontrolled blood pressure who do not meet those criteria (ad never will, due to intolerance/non adherence) and they are susceptible to stroke all the same. They require new approaches. There are also many patients in the UK receiving drugs on the NHS that have not been tested in the scenario of resistant hypertension. Minoxidil, methyldopa, hydralazine, moxonidine and more. None of these have been tested as a fourth line agent in a randomised trial to my knowledge, and none have clinical outcomes data,	Thank you for your comment. The committee has considered this comment and decided not to change the main recommendation as 'special arrangements'. The rationale behind the decision has been added to the guidance (why the committee made these recommendations). The committee has acknowledged that although evidence on its efficacy suggests that it reduces blood pressure in the short- and medium-term, there are uncertainties about how well it works in the long term and whether there are long-term complications. Hypertension can be a lifelong condition, so further evidence generation to establish the long-term outcomes of this procedure is particularly important. The indication for this procedure is specifically 'resistant hypertension' (as currently defined), but section 3.7 has been added to acknowledge the concept of 'resistant hypertension' is evolving and that this procedure may have a role in the treatment of 'uncontrolled hypertension'.

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			and yet all are prescribed and paid for by the NHS to treat uncontrolled and resistant hypertension. The essence of the terms of this IPG are therefore outdated and 2implicitt in my view. With regard to safety, we published a meta analysis led by Dr Ray Townsend in Eurointervention that confirms renal denervation as one of the safest interventional cardiology procedures that we do uin thousands of patients. We also now have 8-year follow-up showing safety and efficacy from an Australian cohort (Schlaich et al, ESH 2022) and we have large scale follow up out to 3 years in the GLOBAL registry. There are many other things that we use and do in interventional cardiology with less robust evidence than this. New TAVI valves and coronary PCI equipment are obvious ones. The IPG says that RCTs and registry analysis are required. These are already done. RADIANCE TRIO is one of the most robust, prospectively powered clinical trials performed to date in hypertension for blood pressure lowering efficacy. GLOBAL 2implicity registry has 3000 patients in it. The UK registry of 253 patients (Sharp, CRC 2016) shows clinically important reductions in blood pressure including on the more robust measure of ambulatory blood pressure monitoring. Given the starting blood pressure of these patients, these were patients with significant unmet clinical need. Patient selection is well described in the SPYRAL and RADIANCE trials and the recent EAPCI/ESC clinical consensus document on renal denervation (Barbato et al, submitted for publication 2022) is clear on selection guidance – BP >140/90 despite three drugs including a diuretic OR patients in whom an expert hypertension centre has proven unable to control blood pressure due to intolerance or other reasons. These are logical indications – if an expert hypertension centre cannot control blood pressure, then the clock is ticking on the risk of cardiovascular events. The next JUKS guidance, of which I will be part and will represent BCIS, will describe the process in detail and will likely include: -Use in expert centres of multidisciplinary teams -Experience and reasonable volumes with the procedures -Ability to deal with the rare complications that may arise -Submission to audit programmes, which will likely be national These recommendations will mirror those of EAPCI/ESC in the upcoming document. NICE have chosen not to fully weight the 'OFF MED' trials of renal denervation because of focus on 'resistant hypertension'. This is not reasonable in my view.	Section 3.5 has been changed to reflect that different devices might have different efficacy and safety profiles. RADIANCE TRIO, GLOBAL simplicity registry (Mahfoud 2019), UK registry (Sharp 2016), and Towensend (2020) were included in the key evidence. SPYRAL ON MED pilot (Mahfoud et al 2022) was included in the appendix. RADIANCE SOLO, RADIANCE II, SPYRAL OFF MED pilot, SPYRAL OFF MED pivotal, Schlaich (2022), Barbato (unpublished), and SPRINT study didn't meet the inclusion criteria.

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			Looking at the Recor programme, OFF MED trials (RADIANCE SOLO) prove a blood pressure lowering effect and on med (TRIO) prove efficacy. What else is there to prove? Longer term maintenance of blood pressure lowering in the RDN arm has been demonstrated out to 2 years in RADIANCE SOLO, but the control arms in these studies have typically changed meds or crossed over, making long-term comparisons against control difficult. It would be unethical to keep patients with uncontrolled pressure in the control arm for several years, given that the SPRINT study showed the beginning of an increase in events from one year onwards in the standard of care arm (BP 136mmHg) versus the intensive control arm (121mmHG). The risk in leaving a control arm with much more elevated blood pressure is now clear, so comparative trials against RDN cannot have prolonged separation of blood pressures out to 3-5 years as we had in the old days – who would want/accept their relatives being left with a BP of 160 for 3 years so we can prove longer term differentials? We imputed longer term efficacy in the SPYRAL ON MED pilot study out to 3 years in the Lancet (Mahfoud et al 2022) and those data, plus the real world 3 year data from GLOBAL, prove longevity of efficacy as well as we can do so in the modern era. The goal of a blood pressure intervention is lower blood pressure at repeat clinic appointments and on out of office monitoring. This has been shown in RDN to the standard required by the FDA for an new blood pressure drug. The irony is that if RDN is not accepted for normal use (within guideline-directed policy limitation documents like the JUKS one we will produce in November 2002) blood pressure clinics will continue to pursue strategies that have barely improved population blood pressure control rates for 40 years. Control rates are around 50% in most countries in the world and are falling in many. Strategies such as weight loss have limited durability of effect. Drugs such as moxonidine, minoxidil, hydralazine will continue to be used despite an absence of outcome data and known adverse side effect profiles that limit the adherence rates to these drugs.	
2.	Consultee 1 NHS professional	1.1	A decision to put RDN in 'special arrangements' allows commissioners not to commission. Let the clinicians define special arrangements and we will. The evidence standard for RDN suggests that NICE should put it in 'normal arrangements' and clinician experts and societies should be the ones defining boundaries, given the epidemic of hypertension associated organ disease – the number one cause of death in the world. Patients need new approaches to the most important disease in medicine – hypertension. They want renal denervation, as proven by Roland Schmeider et al and the Medtronic US patient preference study.	Thank you for your comment. The meaning of 'special arrangements' can be found here: Interventional procedures recommendations | NICE interventional procedures guidance | NICE guidance | Our programmes | What we do | About | NICE The decision to commission or not this procedure is independent of the 'special arrangements' status. It only dictates that if

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				commissioned it requires to continue to collect and review data on the long-term outcomes.
3.	Consultee 2 Ablative Solutions		We would like to bring to the committee's attention a third form of renal denervation delivered with the CE marked Peregrine Catheter. To date, alcohol-mediated renal denervation has been evaluated in open label studies with recent publications on 45 subjects with six and twelve month follow-up data. The therapy is currently being evaluated (through FDA) in a phase III randomised, sham-controlled study on 300 subjects taking 2-5 anti-hypertension medications. Six month efficacy and safety results will be available in Q4 2023. Participating centres are from the US, UK, Ireland, Germany, France, Netherlands, Belgium, and Austria. We would ask the committee to amend the second to last sentence to "It sends radio or sound waves, or delivers medical grade alcohol to destroy the nerves ....."	Thank you for your comment. NICE is producing guidance on this procedure (IP1938), please see https://www.nice.org.uk/guidance/topic-selection/gid-ipg10299
4.	Consultee 2 Ablative Solutions	1.2	Unable to see landing page on point 4	The link to the audit tool will be fixed in the final guidance.
5.	Consultee 2 Ablative Solutions	1.4	Alcohol-mediated denervation is currently being evaluated in the TARGET BP I randomised, sham controlled clinical study (NCT02910414)	Thank you for your comment. NICE is producing guidance on this procedure (IP1938), please see https://www.nice.org.uk/guidance/topic-selection/gid-ipg10299
6.	Consultee 2 Ablative Solutions	2.3	We suggest: The catheter can be connected to a generator to provide energy (delivering Radio Frequency or Ultrasound) or a catheter which can deliver medical grade dehydrated alcohol. All catheters treat from the distal to proximal end of each renal artery.	Thank you for your comment. This will be considered when developing guidance on IP1938.
7.	Consultee 2 Ablative Solutions	3.1	Please consider the following studies for your evaluation of alcohol-mediated renal denervation with the use of the CE mark approved Peregrine Catheter: Mahfoud F, Sievert H, Bertog S, Lauder L, Ewen S, Lengelé J-P, Wojakowski W, Schmieder R, van der Giet M, Weber MA, Kandzari DE, Parise H, Fischell TA, Pathak A, Persu A. Long-Term Results up to 12 Months After Catheter-Based Alcohol-Mediated Renal Denervation for Treatment of Resistant Hypertension. Circ Cardiovasc Interv 2021;14(9):e010075. Mahfoud F, Renkin J, Sievert H, et al. Alcohol-Mediated Renal Denervation Using the Peregrine System Infusion Catheter for Treatment of Hypertension. JACC	Thank you for your comment. These papers will be considered when preparing the overview for IP1938.

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			Cardiovasc Interv 2020; 24;13(4):471-484 Fischell TA, Ebner A, Gallo S, Ikeno F, Minarsch L, Vega F, Haratani N, Ghazarossian VE. Transcatheter Alcohol-Mediated Perivascular Renal Denervation With the Peregrine System: First-in-Human Experience. JACC Cardiovasc Interv 2016;9:589-598. Janas A, Krol M, Hochul M, Jochymczyk M, Hayward-Costa C, Parise H, et al. Evaluation of Transcatheter Alcohol-Mediated Perivascular Renal Denervation to Treat Resistant Hypertension. J Clin Med. 2020;9(6)	
8.	Consultee 2 Ablative Solutions	3.5	Please reference alcohol-mediated renal denervation in addition to radio frequency and ultrasound, as referenced by 3 of the 4 specialists who commented in the Professional Experts' Opinions section (Sept 23rd 2022).	Thank you for your comment. NICE is producing guidance on this procedure (IP1938), please see https://www.nice.org.uk/guidance/topic-selection/gid-ipg10299
9.	Consultee 2 Ablative Solutions	3.6	Alcohol-mediated renal denervation was studied in 45 patients who were taking a mean of 5.1 HTN meds (Circ Cardiovasc Interv. Mahfoud Sept 2021)	Thank you for your comment. This will be considered when preparing the overview for IP1938.
10.	Consultee 2 Ablative Solutions	Lay description	Please consider amending sentence to include alcohol-mediated renal denervation.	Thank you for your comment. This will be considered when developing guidance on IP1938.
11.	Consultee 2 Ablative Solutions	2.3	Please consider amending sentence to include alcohol-mediated renal denervation.	Thank you for your comment. NICE is producing guidance on this procedure (IP1938), please see https://www.nice.org.uk/guidance/topic-selection/gid-ipg10299
12.	Consultee 2 Ablative Solutions	**3.1**	Please consider the following papers relating to alcohol-mediated renal denervation: Mahfoud F, Sievert H, Bertog S, Lauder L, Ewen S, Lengelé J-P, Wojakowski W, Schmieder R, van der Giet M, Weber MA, Kandzari DE, Parise H, Fischell TA, Pathak A, Persu A. Long-Term Results up to 12 Months After Catheter-Based Alcohol-Mediated Renal Denervation for Treatment of Resistant Hypertension. Circ Cardiovasc Interv 2021;14(9):e010075. Mahfoud F, Renkin J, Sievert H, et al. Alcohol-Mediated Renal Denervation Using the Peregrine System Infusion Catheter for Treatment of Hypertension. JACC	Thank you for your comment. These papers will be considered when preparing the overview for IP1938.

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			Cardiovasc Interv 2020; 24;13(4):471-484 Fischell TA, Ebner A, Gallo S, Ikeno F, Minarsch L, Vega F, Haratani N, Ghazarossian VE. Transcatheter Alcohol-Mediated Perivascular Renal Denervation With the Peregrine System: First-in-Human Experience. JACC Cardiovasc Interv 2016;9:589-598. Janas A, Krol M, Hochul M, Jochymczyk M, Hayward-Costa C, Parise H, et al. Evaluation of Transcatheter Alcohol-Mediated Perivascular Renal Denervation to Treat Resistant Hypertension. J Clin Med. 2020;9(6)	
13.	Consultee 2 Ablative Solutions	**2.3**	Prof. Mel Lobo's professional questionnaire, please note he referenced: "There are several different modalities with differing evidence base that include Ultrasound renal denervation and chemical ablation with ethanol which are all transluminal and result in renal sympathetic denervation." In this case chemical ablation with ethanol is alluding to alcohol-mediated renal denervation. Similar to Prof. Lobo, Dr Sen also referenced his involvement "using ethanol" (alcohol-mediated renal denervation) "and ultrasound" Dr Sharp also brings to the attention of the review that there were 3 technologies, Including "Ablative Solutions Peregrine device"	Thank you for your comment. NICE is producing guidance on this procedure (IP1938), please see https://www.nice.org.uk/guidance/topic-selection/gid-ipg10299
14.	Consultee 2 Ablative Solutions	**2.3**	We would like to bring to your attention that Ablative Solutions registered their Peregrine technology with NICE prior to this review and would still welcome the opportunity to comment.	Thank you for your comment. NICE is producing guidance on this procedure (IP1938), please see https://www.nice.org.uk/guidance/topic-selection/gid-ipg10299
15.	Consultee 2 Ablative Solutions	**3.1**	TARGET BP I on med study, (NCT02910414). United States, United Kingdom, Ireland, Germany, France, Netherlands, Belgium & Austria, N=300. Estimated study completion date Q4 2023.	Thank you for your comment. This will be considered when preparing the overview for IP1938.
16.	Consultee 2 Ablative Solutions	**3.1**	Please consider references provided in our previous comments.	Thank you for your comment.
17.	Consultee 3	**2.3**	There is another device used in UK delivering alcohol to destroy the nerves in the renal arteries which should be considered accordingly.	Thank you for your comment.

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				NICE is producing guidance on alcohol-mediated perivascular renal denervation for resistant hypertension (IP1938).
18.	Consultee 3	1.4	To date, alcohol-mediated renal denervation has been evaluated in open label studies with recent publications on 45 subjects with six and twelve month follow-up data. The therapy is currently being evaluated (through FDA) in a phase III randomised, sham-controlled study on 300 subjects taking 2-5 anti-hypertension medications. Six month efficacy and safety results will be available in Q4 2023. Participating centres are from the US, UK, Ireland, Germany, France, Netherlands, Belgium, and Austria. Alcohol-mediated denervation is currently being evaluated in the TARGET BP I randomised, sham controlled clinical study (NCT02910414)	Thank you for your comment. NICE is producing guidance on this procedure (IP1938), and the trial will be considered when preparing the overview.
19.	Consultee 3	2.3	Should be consider alcohol-mediated denervation as well. Example: The catheter can be connected to a generator to provide energy (delivering Radio Frequency or Ultrasound) or a catheter which can deliver medical grade dehydrated alcohol. All catheters treat from the distal to proximal end of each renal artery.	Thank you for your comment. NICE is producing guidance on this procedure (IP1938), please see https://www.nice.org.uk/guidance/topic-selection/gid-ipg10299
20	Consultee 3	3.1	Please consider the following studies for your evaluation of alcohol-mediated renal denervation with the use of the CE mark approved Peregrine Catheter: Mahfoud F, Sievert H, Bertog S, Lauder L, Ewen S, Lengelé J-P, Wojakowski W, Schmieder R, van der Giet M, Weber MA, Kandzari DE, Parise H, Fischell TA, Pathak A, Persu A. Long-Term Results up to 12 Months After Catheter-Based Alcohol-Mediated Renal Denervation for Treatment of Resistant Hypertension. Circ Cardiovasc Interv 2021;14(9):e010075. Mahfoud F, Renkin J, Sievert H, et al. Alcohol-Mediated Renal Denervation Using the Peregrine System Infusion Catheter for Treatment of Hypertension. JACC Cardiovasc Interv 2020; 24;13(4):471-484 Fischell TA, Ebner A, Gallo S, Ikeno F, Minarsch L, Vega F, Haratani N, Ghazarossian VE. Transcatheter Alcohol-Mediated Perivascular Renal Denervation With the Peregrine System: First-in-Human Experience. JACC Cardiovasc Interv 2016;9:589-598. Janas A, Krol M, Hochul M, Jochymczyk M, Hayward-Costa C, Parise H, et al. Evaluation of Transcatheter Alcohol-Mediated Perivascular Renal Denervation to Treat Resistant Hypertension. J Clin Med. 2020;9(6)	Thank you for your comment. These papers will be considered when preparing the overview for IP1938.

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21	Consultee 3	3.6	Alcohol-mediated renal denervation was studied in 45 patients who were taking a mean of 5.1 HTN meds (Circ Cardiovasc Interv. Mahfoud Sept 2021) and should be considered accordingly. There is nothing written in NICE guidance documentation referring that studies need to cover a minimum of patients. 45 patients are powered accordingly for such kind of evidence generation.	Thank you for your comment. NICE is producing guidance on this procedure (IP1938), please see https://www.nice.org.uk/guidance/topic-selection/gid-ipg10299
22	Consultee 4 NHS professional	1.1	I agree that the renal denervation procedures should be undertaken with appropriate goverenance, consent and data collection for audit and research. I am not sure that 'special arrangements' really helps with this process as this may lead to the procedure not being commissioned. This would be disastrous for the UK I am hoping to discuss renal denervation with Prof Nick Linker and want to join up thinking between the Joint UK Societies (which I chair) and NHSE and cardiology commissioning so that pathways for renal denervation can be developed leading to cautious uptake in centres of excellence nationally where patient selection takes place as part of a multidisciplinary approach. This must involve hypertension specialists (of whom there are few in the UK), interventionists as well as the patients themselves.	Thank you for your comment. The committee has considered this comment but decided not to change the recommendation from 'special' arrangements'. The meaning of 'special arrangements' can be found here: Interventional procedures recommendations | NICE interventional procedures guidance | NICE guidance | Our programmes | What we do | About | NICE This recommendation does not per se allow commissioners not to commission but does an enhanced level of surveillance. The rationale behind the decision has been added to the guidance (why the committee made these recommendations'). Please see additional responses to comments 1 and 2.
23	Consultee 4 NHS professional	1.4	Randomised controlled trials of radiofrequency renal denervation, ultrasound renal denervation and chemical denervation with ethanol are currently under way with UK centres participating. There are also planned registries using radiofrequency and ultrasound technologies with UK centres also involved. All trials and registries will report on patient selection, procedural technique and safety and long term efficacy and saefty and quality of life outcomes	Thank you for your comment. NICE is producing guidance on this procedure (IP1938), please see https://www.nice.org.uk/guidance/topic-selection/gid-ipg10299 Once the data from ongoing trials and planned registries is available and published, NICE would be able to consider that evidence should it update this guidance in the future.
24	Consultee 4 NHS professional	1.5	This is of critical importance and the Joint UK Societies will produce a consensus statement pertaining to this matter and this will also outline where renal denervation sits in the management pathway for resistant hypertension.	Thank you for your comment.

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			I would be happy to share a draft of this statement with NICE in advance of publication of your final guidance on renal denervation as it should be ready early 2023.	The committee welcomes and would like to see the draft statement.
25	Consultee 4 22. NHS professional	2.3	Renal denervation can also be achieved with ethanol-mediated sympatholysis (chemical ablation) also delivered via a percutaneous approach. Trials of this technology are currently ongoing.	Thank you for your comment. NICE is producing guidance on alcohol-mediated perivascular renal denervation for resistant hypertension (IP1938).
26	Consultee 4 NHS professional	3.4	In our experience (in Barts Hospital London), and with the use of blinding index questionaires, it is clear that the current procedures for ultrasound and radiofrequency (and alcohol-mediated) renal denervation are all very well tolerated. There is also enormous patient appetite to have the procedure and our centre has had no trouble in recruiting patients into clinical trials of renal denervation.	Thank you for your comment.
27	Consultee 4 23. NHS professional	3.6	Based upon clincial trial data to date, there is sound evidence for the efficacy and safety of the procedure in patients who are unmedicated for hypertension as well as those taking medication and those with resistant hypertension. It would be important to recognise that a number of patients are intolerant to antihypertensive drugs and they may be suitable for the procedure even if they do not fulfil criteria for resistant hypertension as they are at very high cardiovascular risk due to unctontrolled hypertension.	Thank you for your comment. The indication of this procedure is ‘resistant hypertension’. Section 3.7 has been added to the guidance to indicate that the concept of ‘resistant hypertension’ is evolving. Please also see response to comment 1.
28	Consultee 5 24. British Society of Interventional Radiology (BSIR)	1.1 and 1.4	The impact of uncontrolled hypertension is devastating. I believe this procedure maybe promising for select patient groups. Access to a diseased renal artery may still be an issue especially if significant atherosclerotic disease/stenosis, however probably less troublesome than stent deployment and fear of stent migration, mal deployment or poor expansion. The technique it self is nothing new as most interventional radiologists are very familiar with cannulating the renal artery. Many are familiar with sonic waves of lithotripsy, RF ablation techniques though different have similarities and therefore don’t expect a long nor complex operator learning curve. I believe it would be crucial for centres to audit data and collaborate on registries to asses long term results. In some centres where renal stenting is still preformed where criteria is met, may want to see an advantage of this new technique over their existing practice.	Thank you for your comment. Section 3.7 has been added to the guidance.
29	Consultee 6 25. Medtronic Ltd	1.1	Medtronic disagrees with the draft recommendation that renal denervation treatment should only be used with “special arrangements”, based on the Committee’s conclusion that the “evidence on its efficacy is limited in quality”. The full breadth of	Thank you for your comment.

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			evidence has not been appropriately weighted in the Committee's decision-making, and 'standard arrangements' is a more appropriate recommendation for this procedure based on the following key points:	The committee has considered this comment but decided not to change the recommendation from 'special arrangements'. The rationale behind the decision has been added to the guidance.
30	Consultee 6 Medtronic Ltd	3.1	1.Exclusion of relevant evidence in treatment resistant hypertension. The evidence overview relied heavily on the Cochrane review (Pisano et al.). This review focused on treatment resistant hypertension but excluded recent high-quality evidence from the SPYRAL HTN-ON MED study with a treatment resistant hypertension cohort. Since the IPG418 publication there has been substantial evidence demonstrating the long-term effect of renal denervation, including 3-year RCT data, real world data up to 5 years, emergence of long-term data of up to 8 years, and evidence on RDN impact on clinical endpoints. Evidence containing the key outcomes of interest has therefore not been fully considered.	Thank you for your comment. The indication for this procedure is specifically 'resistant hypertension' (as currently defined), but section 3.7 has been added to acknowledge the concept of 'resistant hypertension' is evolving and that this procedure may have a role in the treatment of 'uncontrolled hypertension'. For studies (e.g. SPYRAL HTN-ON MED pilot) that included patents with resistant hypertensin and other forms of hypertension but did not report the efficacy outcomes for resistant hypertension separately were included in the appendix. Detailed rationale can be found in the appendix. Studies included in the appendix were not excluded from the overview. When making decisions, the committee considered the evidence included in the overview in their deliberations.
31	Consultee 6 Medtronic Ltd	General	2.Lack of parity in the evidence appraisal compared with other IPG recommendations. The evidence assessed within the IPG is comparable or superior to that of recent IPGs with 'standard arrangements', and superior to that of other IPGs with 'special arrangements', indicating inconsistency in decision-making (please see evidence grading assessment submitted separately to NICE). We politely request that the Committee reconsiders the quality of the evidence in the context of this evidence	Thank you for your comment. When making decisions for individual procedures, the committee does not only assess the quality and quantity of the evidence for the procedure but also considers how the evidence is situated in a context

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			grading comparison to ensure that the final recommendations are consistent with recent IPG decisions.	specifically for that procedure and relevant population.
32	Consultee 6 Medtronic Ltd	General	3.The weighting and consideration of real world evidence (RWE) Committee decision-making did not sufficiently consider the Global Symplicity Registry (GSR) data and thus was not aligned with the new NICE RWE Framework which states: "Real-world data could be used more routinely to fill evidence gaps and speed up patient access", and "Where data is representative of the target population and of sufficient quality it may be the preferred source of data". The 3-year GSR data indicates that RDN is effective and durable in high-risk populations, including treatment-resistant hypertension, with blood pressure (BP) reductions in these subgroups similar to that observed for the overall GSR cohort. The GSR should be considered as a high-quality evidence source for long-term outcomes and given precedence to in line with the RWE Framework.	Thank you for your comment. Global Symplicity Registry (Mahfoud 2019) was included in the key evidence. When making decisions, efficacy and safety data from a Cochrane review, a meta-analysis and clinical trials, supplemented by observational studies was reviewed by the committee in their deliberations. The committee has explained their rationale in the 'why the committee made these recommendations section': Efficacy and safety data from a Cochrane review, a meta-analysis and clinical trials, supplemented by observational studies (registries) was reviewed by the committee. Evidence on the safety of this procedure suggests that there are no major safety concerns in the short term, and complications are well recognised such as renal artery damage. Evidence on its efficacy suggests that it reduces blood pressure in the short- and medium-term. Overall, there are uncertainties about how well it works in the long term and whether there are long-term complications. So, it should only be used with special arrangements. Hypertension can be a lifelong condition, so further evidence generation to establish the long-term outcomes of this procedure is particularly important.

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33	Consultee 6 Medtronic Ltd	3.2	4. Evidence on clinical outcomes Whilst we appreciate that the reduction of end-organ damage is an outcome of interest, conducting prospective RCTs to demonstrate clinical event reductions is challenging due to practical and ethical reasons. BP is an accepted surrogate endpoint in clinical trials due to the well-established relationship between BP reduction and improved cardiovascular outcomes, and therefore should be the key efficacy outcome.	Thank you for your comment. Further research does not include RCTs only as section 1.3 states that *"Further research should include randomised controlled trials or analysis of registry data"*. 'Reduction in blood pressure' is one of the key efficacy outcomes in section 3.2.
34	Consultee 6 Medtronic Ltd	3.1	5. Upcoming publication The SPYRAL HTN-ON MED pivotal study results will be shared prior to the second Committee meeting; we request that this is given due consideration in the decision-making process as this is a landmark RCT that includes the patient population that is in scope.	Thank you for your comment. The committee has discussed the additional evidence provided by the consultee in part 2 and this has been mentioned in the guidance and overview.
35	Consultee 6 Medtronic Ltd	1.1	In summary, to ensure that the final IPG publication accurately reflect the evidence, we request that: • The draft statement "evidence is limited in quality" is amended to "evidence in the short to medium term is adequate, with long-term evidence emerging". • The IPG recommendations are upgraded from 'special arrangements' to 'standard arrangements'.	Thank you for your comment. The committee has considered this comment and decided not to change the recommendation as 'special arrangements'. The rationale behind the decision has been detailed in the section of 'why the committee made these recommendations'.
36	Consultee 7 ReCor Medical Inc.	1.1	ReCor Medical, Inc. request that the IPAC committee consider changing the draft recommendation for percutaneous transluminal renal sympathetic denervation for resistant hypertension procedures to 'standard arrangements' instead of 'special arrangements' at its meeting in December. The justification for this, in short is that the committee did not have all relevant evidence available, and the evidence of obsolete first-generation devices and poorly designed studies was weighted heavily in the literature review. Six robust randomized controlled trials (most of which sham-controlled), designed to address confounding and blinding challenges identified as significant flaws in the studies of first-generation renal denervation devices have demonstrated clinically meaningful blood pressure reductions with renal denervation.	Thank you for your comment. The committee has considered this comment and decided not to change the main recommendation as 'special arrangements'. The IP programme looks at procedures but not the devices used. The indication of the procedure is 'resistant hypertension'. Extra wording has been added to section 3.5 and section 3.7 has been added to the guidance.

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				For studies that included patents with resistant hypertensin and other forms of hypertension but did not report the efficacy outcomes for resistant hypertension separately were included in the appendix. Detailed rationale can be found in the appendix. Studies in the appendix were not excluded from the overview.
37	Consultee 7 ReCor Medical Inc.	3.1	The IPAC rapid literature review failed to include all the evidence for second-generation renal denervation devices (ultrasound and radiofrequency). Further, the committee have generalised evidence from first-generation renal denervation studies to the second-generation RF and ultrasound devices. This is neither appropriate nor clinically relevant given that first-generation renal denervation systems are now obsolete and not available for clinical use. The evidence which IPAC considered is biased towards outcomes from first generation devices which are no longer clinically relevant. The implications of this are important for two reasons: 1) Significant Improvements in the design of second-generation renal denervation devices and refinement of procedural technique over time, and 2) Significant improvements in clinical trial design to address well-documented confounding factors in first-generation renal denervation studies with blood pressure reduction as the primary endpoint. Specifically, the rapid literature review for IPAC failed to identify a 12-month Paradise™ multi-centre ultrasound renal denervation system observational study (ACHIEVE). (Daemen et al. 2019)	Thank you for your comment. The IP programme looks at procedures but not the devices used. The indication of the procedure is 'resistant hypertension'. Extra wording has been added to section 3.5. Daemen (2019) was included in the appendix and this paper was not excluded from the overview.
38	Consultee 7 ReCor Medical Inc.	3.1	Since the rapid literature review cut-off date (March 30, 2022), additional relevant clinical data have been published, demonstrating long-term durability of the blood pressure-lowering effects of the Paradise™ ultrasound renal denervation and other renal denervation systems; Zeijen et al. at 5 years (Zeijen et al. 2022b), RADIANCE-HTN TRIO at 6 months (Azizi et al.(a) draft manuscript) and 2 years (Bloch et al. 2022) and RADIANCE-HTN SOLO at 3 years (Rader et al. 2022), one study for the Symplicity Spyral™ radiofrequency renal denervation system (SPYRAL HTN-ON MED pilot) has since reported durability data at 3 years. (Mahfoud et al. 2022).The blood pressure-lowering effect with Paradise™ ultrasound renal denervation system is durable with data out to 3 years in RADIANCE-HTN-SOLO (Rader et al. 2022), and 2 years in RADIANCE-HTN-TRIO. (Bloch et al. 2022) This evidence is supported by a recently published paper demonstrating durability of the blood-lowering effect of	Thank you for your comment. REQUIRE (Kario 2022), Pisano (2021) and Townsend (2020) were included in the key evidence. Daemen (2019), Mahfoud (2022) and Sardar (2019) were included in the appendix. RADIANCE-HTN SOLO (Azizi 2018, 2019; Rader 2022), Kario (2021), Bloch (2022), Weber (2021) and Rahimi (2021) didn't meet the inclusion criteria.

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			the Paradise™ ultrasound renal denervation system and other renal denervation systems out to 5 years. (Zeijen et al. 2022b)	Bruno (2020); Zeijen (2022b); Rodríguez-Leor (2022) have been added to the overview.
39	Consultee 7 ReCor Medical Inc.	3.5	In recognition of the strength of clinical evidence of clinical benefit and strong safety profile from second-generation clinical studies, the European Society of Hypertension (ESH) (Schmieder et al 2021), the European Society of Cardiology (ESC) Council on Hypertension and the European Association of Cardiovascular Interventions have all recommended the use of renal denervation in adult patients with uncontrolled hypertension despite optimal medical management (see further comments in Section 3.1). In addition, a growing number of National professional Medical Society Consensus Statements have shifted from recommending renal denervation 'only in research' to 'routine clinical use' in recognition of the robust clinical data supporting efficacy and safety of renal denervation in the presence or absence of anti-hypertension medications. Notably, Spain, Italy and most recently the Netherlands (Bruno et al. 2020; Rodríguez-Leor et al. 2022; Zeijen et al. 2022a) have all opted to recommend renal denervation for eligible patients.	Thank you for your comment. Schmieder 2021 and Williams (2018) were included in the existing assessment. Bruno (2020); Zeijen (2022a) and Rodríguez-Leor (2022) have been added to the overview.
40	Consultee 8 Hull University Teaching Hospitals NHS Trust		Further RCT data has become available on specific patient subsets whom continue to present therapeutic challenge for the management of their hypertension – foremost are patient who cannot or will not take any medication. These are a sizeable cohort in contemporary practice and have previous been entirely un-represented in trials of anti-hypertensive treatment. This patient group are high risk or target organ damage, not amenable to conventional therapy, and disenfranchised from almost all evidence base of hypertension treatment. The Spyral 'Off Meds' trial start to give wider therapeutic options to these patients, and shows a significant reduction in systolic and diastolic blood pressure – this is likely to translate into overall risk reduction in hard endpoints for this group. As a clinical cardiologist performing RDN – this is a valuable option for this patient group and my contention is that we can make RDN more widely available for this limited group. A key step is ascertaining the reasoning and rationale–for why the patient cannot or will not take medication (an area itself that is under-researched) – but putting that aside – this group of patients exist, and in the 'real world' are relatively prevalent. I would support making RDN available to some limited extent to this patient population, whilst promoting the collation of more observational data around the causes and triggers for lack of tablet taking in this group – a two pronged approach to gaining a greater understanding in tham.	Thank you for your comment. The indication of this procedure is 'resistant hypertension'. Section 3.7 has been added to the final guidance. Please see additional responses to comments 1, 2 and 32. SPRYAL OFF MED trial – did not meet the inclusion criteria.

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41	Consultee 9 Thrombosis UK		Many thanks for your email and your invitation to comment on this interventional procedure. Unfortunately, we will be declining this invitation as it falls outside the remit of the charity's work which is education and awareness of venous thromboembolism.	Thank you for your feedback.
42	Consultee 10 ARRHYTHMIA ALLIANCE	1.1	Currently in England, for every 10 people diagnosed with Hypertension, 7 remain undiagnosed and oblivious of their Uncontrolled Resistant Hypertension. For these patients, the first experience they have of their Uncontrolled Resistant Hypertension is when they experience, often a life changing, adverse cardiovascular event as a result of their undiagnosed Hypertension. People with Uncontrolled Resistant Hypertension have double the risk of cardiovascular events than those who have their Hypertension under control. This means that patients with Uncontrolled Resistant Hypertension are twice as likely to suffer from illnesses such as strokes, myocardial infarctions, heart failure and chronic kidney disease. Hypertension alone accounts for 12% of primary care visits and a staggering £2.1 bn of annual NHS spend. The increased likelihood of adverse cardiac outcomes and the massive impact of Hypertension on the NHS alone, should make us consider all treatment options available to alleviate this NHS burden and importantly improve patient outcomes wherever possible. 2020 evidence from the University of Warwick shows that 55% of hypertensive patients are either partially or entirely nonadherent to pharmacological solutions to treat their Hypertension. We believe therefore access to all treatment options to improve patient outcomes (and reduce unnecessary costs to the NHS) should be considered and made available to those that do not respond to drug treatments and are suitable for Renal Denervation.	Thank you for your comment. The indication of this procedure is 'resistant hypertension', and section 3.7 has been added to the guidance. Please see additional responses to comments 1, 2 and 32.
43	Consultee 11 British and Irish Hypertension Society	General	I have read all 121 pages of the Evidence Review Only 3 trials are of importance to me. The registries and observational studies do not reliab15mportantify benefit, but can inform safety. It is safe, but severe stenosis runs at about 0.5% within 18 months. There are two conflicting, sham-controlled RCTs. Both short. One international and positive and the other Japanese and plumb negative. I think benefit is not reliably demonstrated and so continuing to encourage use in trials makes sense. A 3-way randomised trial compared radiofrequency ablation of the main artery only, the main and branch arteries and US ablation. Arguably US came out on top. We still don't know the best kit to use and this is complicated by the market dominance of the radiofrequency ablation device companies.	Thank you for your comment. Section 2.1 states: "…Hypertension is considered resistant if it is not controlled after treatment with at least 3 antihypertensive medications from different classes." To align with NICE'S guideline, section 2.2 describes: "NICE's guideline on hypertension in adults describes diagnosing and managing hypertension, including resistant hypertension."

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			A subanalysis suggested that benefit was best at highest BPs (180 plus I think) and another suggested improved results if those patients with hyperaldosteronism were excluded. NICE used a cut down ESC 2013 definition of resistant HT, not defining the BP (just remaining elevated rather than over 140/90) and the didn't mention that one agent should be a diuretic. In my view the benefit of RDN is still in doubt and we should continue to offer it as part of a trial. Trials should be sham-controlled with efforts to check adherence at point of recruitment and during the trial. Blinding should be checked during the follow-up and trial follow-up needs to be a deal longer than 6 months. It could be justifiable for those with uncontrolled HT (.160, >180?) despite 3 or more full-dose, complimentary agents one a diuretic, providing outcomes are monitored as with SITS-MOST in stroke. One of our members emphasised that registers and observational studies were still valid, to help focus research questions. I hope these comments are helpful to the review process, which we will happily support in any way we can.	

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."