NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: **IP923/2 Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension**

Your information

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Nominated/ratified by (if applicable):	BCIS
Registration number (e.g. GMC, NMC, HCPC)	GMC 4530660

How NICE will use this information: the advice and views given in this questionnaire will form part of the information used by NICE and its advisory committees to develop guidance or a medtech innovation briefing on this procedure/technology. Information may be disclosed to third parties in accordance with the Freedom of Information Act 2000 and the Data Protection Act 2018, complying with data sharing guidance issued by the Information Commissioner's Office. Your advice and views represent your individual opinion and not that of your employer, professional society or a consensus view. Your name, job title, organisation and your responses, along with your declared interests will also be published online on the NICE website as part of the process of public consultation on the draft guidance, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.

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☒ I give my consent for the information in this questionnaire to be used and may be published on the NICE website as outlined above. If consent is NOT given, please state reasons below:

Click here to enter text.

Please answer the following questions as fully as possible to provide further information about the procedure/technology and/or your experience.

Please note that questions 10 and 11 are applicable to the Medical Technologies Evaluation Programme (MTEP). We are requesting you to complete these sections as future guidance may also be produced under their work programme.

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? – Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? – Is this procedure/technology performed/used by clinicians in specialities other than your own? – If your specialty is involved in patient selection or referral to another specialty for this	I have 11 years of experience of selection and treating patients with renal denervation and am regarded as an international authority in this area. I have recruited to sham-controlled, international, randomised trials of renal denervation, including SPYRAL OFF-MED pilot, SPYRAL ON-MED pilot, SPYRAL OFF MED pivotal, SPYRAL ON MED continuation study, RADIANCE SOLO, RADIANCE TRIO, RADIANCE II I have also recruited to non-randomised trials of renal denervation: SYPRAL DYSTAL, GLOBAL Symplicity registry I am a member of the steering committee of the Recor RADIANCE research programme I am global co-principal investigator of the Medtronic SPYRAL DYSTAL study I founded, led and reported the results of the UK Renal Denervation Affiliation – an investigator-led group that reported what, to my knowledge, remains the largest investigator-led registry of results from this technology to date. It was reported in the German national cardiac journal, Clinical Research in Cardiology. I have contributed to national and international consensus documents on the use of this technology. *Have you used it or are you currently using it?* Yes, I am an expert in the use of the Medtronic SPYRAL and the RECOR Paradise renal denervation systems. I have recruited to trials of both technologies, as a specialist running a hypertension clinic and as an interventional cardiologist doing the procedure myself.

	procedure/technology, please indicate your experience with it.	– *Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake?* There is substantial unmet need for hypertension devices. Blood Pressure control rates for hypertension in the UK vary according to report, but the average comes out at approximately 50% when a standard of 140/90 is used. This means that millions of patients in the UK currently have uncontrolled hypertension. Given that Hypertension is the number one modifiable risk factor for death, stroke, heart failure and myocardial infarction in the world, and remains a substantial source of healthcare burden in the UK, the potential pool of patients is significant, and the monetary cost of the current unsuccessful strategies used to control hypertension is substantial. Control rates have not significantly improved in developed countries for decades despite many groups of effective medicines, suggesting techniques/treatments for controlling hypertension are required. Speed of uptake could be significant if this was funded and approved as the skills as easily trainable and acquired. There are over 700 UK interventional cardiologists who could learn this procedure in a matter of weeks/months, as could several hundred interventional radiologists. The facilities required to perform this procedure are the same for a coronary or renal angiogram and are present in most district general hospitals and all tertiary centres in the UK. – *Is this procedure/technology performed/used by clinicians in specialities other than your own?* Currently, after the UK Joint Society Guidance on Renal Denervation (Lobo, Sharp et al Heart 2019), very few patients are being treated with this technology clinically, outside of a clinical trial or registry in the UK. I would estimate fewer than 30 cases per year. - *If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.*

		Patient selection should be by someone who regularly sees hypertension patients in a clinic environment. That may be a cardiologist, nephrologist, clinical pharmacologist, endocrinologist, elderly care doctor, general physician or GP with a special interest. In my practice to date, patient selection has been done my me and/or a nephrologist or second cardiologist who worked with me on my research programme.
2	– Please indicate your research experience relating to this procedure (please choose one or more if relevant):	I have done bibliographic research on this procedure. – YES, I have contributed to the Academic Research Consortium position statement on research trials in Renal Denervation, amongst other things. I have done research on this procedure in laboratory settings (e.g. device-related research). – YES – I have recruited to the recent pivotal sham-controlled trials of RDN and treated these patients in those studies I have done clinical research on this procedure involving patients or healthy volunteers. – YES – As above I have published this research. – YES, I have co-authored several publications in The Lancet on the use of this technology Other (please comment)
3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	It is an entirely novel concept compared to current practice. The current two pillars of hypertension care are lifestyle modification and then pharmacology. These strategies are currently controlling about half of patients with hypertension in the UK. Renal denervation is a one-off procedure that offers blood pressure reduction superior to that of salt reduction out to a time horizon that currently appears to be beyond three years (as reported in the GLOBAL Symplicity Registry) and has recently been reported in from an Australian group to persist out to ten years in one of the earliest treated human cohorts. In theory, and on the basis of

		pre-clinical work shortly to be published by Sharp et al in the Journal of Hypertension, the denervation effect should be permanent. This would be considered the first in a new class of procedure, as the technology never really gained a clinical hold in the UK and the current iterations of the devices are novel
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	It could replace the standard of care in patients with mild hypertension. If a patient had a new diagnosis of hypertension with a blood pressure of, for example, 150/95 after efforts at lifestyle modification, renal denervation could be offered and would have a reasonable chance of getting many of those patients to control standard of 140/90, given that in the real-world GLOBAL REGISTRY, the average office systolic blood pressure reductions gained were -16.5 ± 28.6 mmHg at three year follow up (Mahfoud et al. Eur Heart J 2019 Nov 1;40(42):3474-3482. doi: 10.1093/eurheartj/ehz118). These values are in line with the recently published three-year follow-up from the SPYRAL ON MED pilot, published in the Lancet, whereby the systolic ambulatory blood pressure reduction at 3 years was approximately 10mmHg. However, I suspect clinical recommendation from expert groups will be that focus should be initially on those patients who are failing to get to control with current strategies, and therefore it will initially be used as an addition to standard of care, rather than replacement for it.

Current management

5	Please describe the current standard of care that is used in the NHS.	1. Lifestyle modification – e.g. weight loss, salt reduction, alcohol reduction, exercise 2. Pharmacology – use of ACE inhibitors, calcium channel blockers and diuretics in the first instance, but there are many more drugs available with increasingly smaller incremental effectiveness as they are added at 5th/6th/7th line etc

6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	There are currently three renal denervation technologies in clinical trials in the UK. Medtronic SPYRAL, Recor Paradise, and Ablative Solutions Peregrine device. There are other device-based therapies under investigation internationally, including baroreceptor modification devices, carotid body deformation (Mobius device) and the backbeat pacemaker device. Clinical data on these devices are not as developed as they are for RDN and effectiveness is uncertain for all three types.

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Better rates of blood pressure control, leading to fewer strokes, heart attacks, heart failure patients and death. A reduction in office systolic blood pressure of 10mmHg would be expected to reduce events by 27% for stroke and 28% for heart failure (Ettehad, Lancet , 2016) amongst other potential benefits. It has been widely accepted, including by the USFDA and the EMA, that any mechanism of blood reduction will have similar benefits, and so office blood pressure is seen as an acceptable surrogate for clinical event reduction by international regulators.
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Those most in need currently are those who have significant elevation of blood pressure despite attempts at lifestyle modification, pharmacological strategies and have seen a hypertension specialist and had secondary causes of hypertension excluded. Uncontrolled blood pressure may be because of medication resistance or intolerance. The latter is a bigger clinical problem in the UK than the former, depending on how one defines each concept.
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Yes. It could substantially reduce the number of GP appointments in primary care, as blood pressure may be reduced from a single procedure taking less than one hour to perform. Currently, pharmacological approaches require repeated consultations. It could also lead to fewer heart attacks, strokes, heart failure, renal failure patients attending primary, secondary and tertiary care, as one would expect from blood pressure reductions as described in the second generation of RDN sham-controlled trials that have been reported since 2017. It would not lead to less invasive treatment in the first instance, as this would be the first approved treatment for hypertension that is invasive, though the net number of lifetime invasive procedures for any given patient may decrease, as there would be expected to be fewer myocardial infarctions requiring coronary stent procedures, heart failure patients requiring pacemaker devices, stroke patients requiring thrombectomy etc. Each patient might have more than one of these CV event-related procedures within their lifetime according to the degree of hypertension associated end organ damage whereas renal denervation will only be performed once.

10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	It would cost more initially, as the procedure cost would be something approaching £5000-£7000, but that also has to be set against the likely reductions in highly costly clinical events, which in hypertension can occur within a relatively short time horizon for patients with other cardiovascular risk factors. In the SPRINT hypertension study, event curves began to separate after just one year and mortality curves separated in less than three years when blood pressure lowering strategies were tightened in one arm. Work I have presented at the EuroPCR 2022 international conference (it will be published in late 2022 once we can update the model with the results from the upcoming SPYRAL ON MED continuation study results) suggest the ICER is within acceptable boundaries at £7169, based on the six-month results of the SPYRAL ON MED pilot study, published in the Lancet in 2018 by Kandzari et al. If we updated the model using the three years results, published in 2022 by Mahfoud et al in the Lancet, the ICER would be substantially lower than this, given the effect size was larger in that longer term follow up paper. (Copy of the poster presentation from that conference is attached at the end of this document) There would, currently, be restrictions on the amount of catheter laboratory time available for this procedure in the UK, though if heart attacks, heart failure and stable ischaemic heart disease PCI procedures were subsequently reduced, that would be partially offset. It is likely that cath lab time would be the 'rate-limiting step' for this procedure in its infancy though. Currently, hypertension medicines are extremely cheap to prescribe, but are also extremely costly as a strategy, in that they only achieve their goals in half of patients – of getting patients to a blood pressure control standard of even 140/90 (some countries are now aiming for 130/80) – leading to a global epidemic of hypertension associated cardiovascular adverse events and making hypertension the number one modifiable cause of death globally. Even if we inflate rates of blood pressure control to 70%, that would still leave millions of patients with uncontrolled blood pressure in the UK.
11 - MTEP	What do you consider to be the resource impact from adopting this	It would cost more initially, as the procedure cost would be something approaching £5000-£7000, but that also has to be set against the likely reductions in highly costly clinical events,

	procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	which in hypertension can occur within a relatively short time horizon for patients with other cardiovascular risk factors. In the SPRINT hypertension study, event curves began to separate after just one year and mortality curves separated in less than three years when blood pressure lowering strategies were tightened in one arm. Work I have presented at the EuroPCR 2022 international conference (it will be published in late 2022 once we can update the model with the results from the upcoming SPYRAL ON MED continuation study results) suggest the ICER is within acceptable boundaries at £7169, based on the six-month results of the SPYRAL ON MED pilot study, published in the Lancet in 2018 by Kandzari et al. If we updated the model using the three years results, published in 2022 by Mahfoud et al in the Lancet, the ICER would be substantially lower than this, given the effect size was larger in that longer term follow up paper. (Copy of the poster presentation from that conference is attached at the end of this document)
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	A catheter laboratory, as are currently used and staffed for coronary angiogram or renal angiogram procedures. No hardware modifications are required. The procedure requires a small portable energy generator which is easily acquired and stored (similar to the generator required to power ablations of atrial fibrillation)
13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Yes. The procedure requires theoretical and technical training. I have trained a number of people in both of these aspects for several years. The procedure is on the less complex end of the interventional medicine spectrum, with a learning curve that is short, depending on operator prior experience of renal interventions. It is expected that after ten procedures, most operators will be technically proficient.

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence:	There have been few adverse events reported in the second generation of sham-controlled clinical trials. The main complication risks are:

	Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	1. Femoral arterial access site complications. These are common to any interventional procedure requiring arterial access with a 6 French sheath and are typically quoted as a 1 in 500 risk serious vascular injury requiring either surgical or percutaneous repair. 2. Sedation related complications. The procedure does require analgesia and sedation as it causes pain during activating of energy delivery. The frequency of such complications are well described in the literature. 3. Renal artery guiding catheter/wire dissection/new renal artery stenosis. The frequency of this was reported in a manuscript I co-authored in Eurointervention 2020 (Townsend et al) and is low at 0.45%. Much of that was progression of native renal arterial disease which would be expected to be similar frequency in a procedure-naïve population. It is treatable with renal artery stenting as required.
15	Please list the key efficacy outcomes for this procedure/technology?	The key efficacy outcomes are those of office and ambulatory systolic blood pressure reduction, as described in the following second-generation sham-controlled studies: SPYRAL OFF MED Pilot (Townsend Lancet 2017) SPYRAL ON MED Pilot (Kandzari Lancet 2018; Long-term follow up Mahfoud Lancet 2022) SPYRAL OFF MED pivotal (Bohm Lancet 2020) RADIANCE SOLO (Azizi Lancet 2018) RADIANCE TRIO (Azizi Lancet 2021) Earlier sham-controlled trials used now redundant technologies and techniques and are therefore no longer relevant (much as in the field of stroke mechanical thrombectomy trial designs/technologies and results were radically different from 2014 onwards) The blood pressure reductions gained vary from 4 to 10mmHg on ambulatory and office systolic blood pressure in these sham-controlled trials. The blood reductions gained appear closely correlated to starting blood pressure across a number of studies and this new generation of trials looked only at mild-moderate starting blood pressure values to limit variability. Real world results of patients treated with RDN are therefore larger, as starting blood pressures are higher.

		- Mahfoud et al. Eur Heart J 2019 Nov 1;40(42):3474-3482. doi: 10.1093/eurheartj/ehz118 - Sharp et al. Clin Res Cardiol. 2016; 105: 544–552.
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	There is a 'non-responder' rate of between 25 and 33%, defined as a blood pressure reduction of less than 5mmHg on ambulatory monitoring. Reasons for that are thought to include – lack of association of the sympathetic nervous system with that patient's hypertension; insufficient energy delivery and therefore ablation of renal nerves; compensatory responses that restore blood pressure. This responder rate is favourable when compared to existing cardiovascular devices, such as atrial fibrillation ablation and cardiac resynchronisation therapy. It is similar to the reported rates of angina response following PCI for stable ischaemic heart disease. The longest follow-up available is approximately ten years on a human cohort and was recently reported at the European Society of Hypertension by Schlaich et al. Whether the blood pressure response remains significant beyond that is uncertain. Large scale reporting of over 1000 patients from the GLOBAL registry suggests efficacy is maintained beyond 3 years (Mahfoud et al. Eur Heart J 2019 Nov 1;40(42):3474-3482. doi: 10.1093/eurheartj/ehz118) The rate of renal artery injury has been reported in a large meta-analysis (Townsend et al, Eurointervention, 2020) The ambulatory blood pressure effect size in the real world is larger than the effect seen in randomised trials. This is likely because patients treated in the real world have higher starting blood pressures.
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	This technology had a failed trial in 2014 – Symplicity HTN-3 (Bhatt et al, NEJM 2014), using the first generation of catheter (Symplicity Flex), the first generation of technique (proximal renal artery ablation) and performed by operators with no prior clinical experience and very low volumes of doing this procedure by the end of the trial. Medication changes occurred in approximately 40% of patients between their procedures and the six-month primary endpoint,

		against protocol, thus potentially confounding the results. This has been analysed and explanations proposed by Kandzari et al in the European Heart Journal (https://academic.oup.com/eurheartj/article/36/4/219/2293381) Since this trial, the catheters have been redesigned, the technique is entirely different (43 points of ablation in the second generation SPYRAL trials, as opposed to 11 points of ablation in Symplicity HTN-3) and the patient population different. This partly explains the success of the second-generation trials compared to the variability of the first.
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	It is safe enough to be carried out in most district general hospitals in due course. Patient screening and selection requires a hypertension specialist clinic and safe procedural delivery requires a catheter laboratory.

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Schlaich et al European Society of Hypertension 2022 – 10 yr follow up of a cohort of patients undergoing renal denervation Sharp et al EuroPCR 2022. Cost-effectiveness analysis of radiofrequency renal denervation in a UK setting Esler et al European Society of Hypertension 2022. Clinical Event Reductions In High-risk Hypertension Patients Treated With Renal Denervation: 10-year Projections Based On 3-year Follow-up From The Global SYMPLICITY Registry Sharp et al Histological evidence supporting the durability of successful radiofrequency renal denervation in a normotensive porcine model (accepted for publication in the Journal of Hypertension 2022. Should be available online in August 2022)
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Yes SPYRAL ON MED sham-controlled trial continuation is expected to report in late 2022 (estimated October)

		RADIANCE II is expected to report in late 2022 (estimated October) Both are large trials of RDN including over 200 patients. They are likely to be the final sham-controlled trials of these two technologies if those trials are positive. TARGET BP 1 is currently recruiting, using the Peregrine catheter.

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	There are approximately 18 million patients in the UK with hypertension. Up to half of those are uncontrolled. The pool of patients who might be suitable for this procedure is therefore extremely large. In reality, many would not be appropriate, many would not want it (approximately one third of German patients would want an RDN procedure in a paper by Schmeider et al Clin Res Cardiol 2019 Dec;108(12):1331-1342.) and restrictions would be required. If the pool was restricted to those with 'resistant hypertension' – patients with a BP >140/90 despite 3 or more medications - that is thought to be between 2 and 12% of the hypertensive population. We are therefore potentially looking at several hundred thousand patients, of whom only a third might want treatment. An unrestricted service for 'resistant hypertension' would therefore easily have over 100,000 potential candidates for treatment.
22	Are there any issues with the usability or practical aspects of the procedure/technology?	The procedure is relatively simple and is within the skillset of most/all interventional cardiologists and radiologists. The workflow is simple and the procedure takes under one hour in most cases.
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Availability of catheter laboratory space and upfront cost of the procedure vs 3-10yr time horizon gain are the main barriers to widespread adoption.

24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	A long-term outcomes trial is often proposed as a necessity, but it is not feasible in the contemporary era due to the level of residual risk on a per-patient basis. It would involve the largest device trial in the history of cardiovascular medicine with a sample size approaching 20,000 patients, with a prohibitive cost and considerable risk of a confounded outcome now that patients can take their own blood pressure at home. It would also expose a control arm to known risk over a long period of time. The reason that the current generation of OFF MED RDN trials has a short period of follow-up is due to the known risk of leaving patients with uncontrolled blood pressure beyond one year. The standard for new antihypertensive medicines is to prove efficacy in an 'OFF-MED' format out to 12 weeks, and then larger comparative studies or single arm studies showing efficacy. There are also many drugs currently being used for hypertension that do not have outcome trial data, including spironolactone (the fourth line drug in the NICE hypertension algorithm) doxazosin, minoxidil, hydralazine and more. Renal denervation has some of the highest quality cardiovascular device research trials ever conducted, with four sham-controlled studies showing efficacy with two separate devices tested by two separate research groups. That sort of effectiveness data is unprecedented.
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post	Beneficial outcome measures: Expected reductions in ambulatory systolic blood pressure of >5mmHg should be achieved in over 60% of patients treated Adverse outcome measures: Serious complication rates of under 1% for vascular surgical intervention/renal artery stenting/major bleeding

	procedure timescales over which these should be measured:	

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	This new area of medicine has challenged orthodoxy and met considerable resistance. This has been good for the field, as it has led to some of the highest quality clinical trials in the history of device medicine which have now convincingly proven the efficacy of the Medtronic SPYRAL and the Recor Paradise technologies. The arguments against this technology seem to be: 1. The effect size is not large enough (but it is larger than that of moderate salt reduction in the recent sham-controlled studies and the benefits of salt reduction are not seriously questioned. The benefits in real world patients are large, sa seen in the GLOBAL registry) 2. It doesn't work in everyone (response rates of approximately 66% are similar to that of CRT pacemakers and better than that of AF ablation) 3. We don't need it, we have drugs which are cheap (we have had over 15 different drugs for hypertension for decades – we have more than enough drugs, yet still, control rates globally are below 60% in whichever healthcare system they are used) 4. We do not have a cardiovascular outcomes trial (we do not need one for any new anti-hypertensive drug and blood pressure reduction improves outcomes whether by lifestyle modification or drugs. Devices are unlikely to be different and this is why the FDA and EMA allow BP reduction as a surrogate trial endpoint.) 5. It is invasive and that is unpleasant (that is for patients to decide – a third of them wanted it in a well conducted survey by Roland Schmeider in Germany) 6. It is invasive and bad things may happen (the rates are less than 1% and the BP reductions achieved would be expected to reduce cardiovascular events by an actual risk of 11% and relative risk of 26% at 10 years on recently reported work (see attached abstract poster below from Kandzari et al for a summary of the findings – reported at the US Society of Cardiac and Angiographic Interventions (SCAI) in May 2022) 7. It is expensive (the cost effectiveness analysis for a conservative real world effect size of 6.8mmHg shows an ICER of £7,169. A highly cost-effective intervention)

		8. We don’t have the operators to do this (we didn’t have the operators for TAVI or CRT until we trained them. Hospitals will always have to react to new transformative treatments) 9. Some of the older trials with redundant technologies and techniques did not show efficacy (same as with stroke mechanical thrombectomy, our understanding of anatomy and selection is much improved now, with better devices giving a much larger ‘dose’ of energy to the renal nerves) 10. Hypertension specialist clinics are in short supply (yes, and that is unacceptable. This technology will actually drive up the supply of hypertension experts and will likely improve the care across the board for hypertension, as a new raft of physicians will have another reason to bring their skills to these patients. Algorithms related to who can have this procedure could help drive across the board improvements in care).

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Declarations of interests

Please state any potential conflicts of interest relevant to the procedure/technology (or competitor technologies) on which you are providing advice, or any involvements in disputes or complaints, in the previous **12 months** or likely to exist in the future. Please use the NICE policy on declaring and managing interests as a guide when declaring any interests. Further advice can be obtained from the NICE team.

Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Direct - financial	Consultant/Lecture Fees: Medtronic, Recor Medical, Boston Scientific, Philips, Penumbra	**Medtronic (before 2016)** **Recor Medical (before 2016)** **Boston Scientific (2019)** **Philips (before 2016)** **Penumbra (2020)**	**All are ongoing**
Choose an item.			
Choose an item.			

☒ I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during the course of my work with NICE, must be notified to NICE as soon as practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate and timely declarations then my advice may be excluded from being considered by the NICE committee.

Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**Andrew Sharp**

Dated:	**12/7/22**

NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: **IP923/2 Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension**

Your information

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Email address:	[redacted]
Professional organisation or society membership/affiliation:	BCIS
Nominated/ratified by (if applicable):	Click here to enter text.
Registration number (e.g. GMC, NMC, HCPC)	6079534

How NICE will use this information: the advice and views given in this questionnaire will form part of the information used by NICE and its advisory committees to develop guidance or a medtech innovation briefing on this procedure/technology. Information may be disclosed to third parties in accordance with the Freedom of Information Act 2000 and the Data Protection Act 2018, complying with data sharing guidance issued by the Information Commissioner's Office. Your advice and views represent your individual opinion and not that of your employer, professional society or a consensus view. Your name, job title, organisation and your responses, along with your declared interests will also be published online on the NICE website as part of the process of public consultation on the draft guidance, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.

For more information about how we process your data please see our privacy notice.

X I give my consent for the information in this questionnaire to be used and may be published on the NICE website as outlined above. If consent is NOT given, please state reasons below:

Click here to enter text.

Please answer the following questions as fully as possible to provide further information about the procedure/technology and/or your experience.

Please note that questions 10 and 11 are applicable to the Medical Technologies Evaluation Programme (MTEP). We are requesting you to complete these sections as future guidance may also be produced under their work programme.

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? – Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? – Is this procedure/technology performed/used by clinicians in specialities other than your own? – If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	Over 10 years of experience with the technology and performing the procedure. Investigator in all SYPRAL Trials. Lead for RDN (renal denervation) at Imperial NHS Trust research program. Principal Investigator in 1 investigator led RDN study. GSR DEFINE Investigator. Investigator in clinical trials using Ethanol (ABLATIVE SOLUTIONS) and ultrasound based (RECOR) denervation catheters RDN is currently primarily used in the context of clinical trials or as part of a registry in a small proportion of hypertension patients. The procedure is safe, easy to perform and should be feasible as a day case procedure in more experienced hands. Given its ease of use and the shear number of patients with resistant hypertension/ patient intolerant of multiple medications there is significant potential for rapid uptake. However the clinical trials clearly demonstrate that the effect of an RDN procedure is dependent on the number of ablations and the experience of the operator. To ensure the best outcomes for the treatment the expansion of this technology should be to centres with established experience with the procedure and have contributed to the clinical trials establishing the technology.
2	– Please indicate your research experience relating to this procedure	I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research.

	(please choose one or more if relevant):	
3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	The technology is innovative but has been around the clinical domain for over a decade now. It has been established as a safe procedure with very low rates of complications. Established practice and no longer new.
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Addition to existing standard of care

Current management

5	Please describe the current standard of care that is used in the NHS.	Dietary, lifestyle advice. Pharmacotherapy. Specialist clinics
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	No

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Better blood pressure control. Fewer complications from hypertension. Lower rates of renal failure, heart failure, myocardial infarction and stroke.
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Drug resistant hypertensives Patients intolerant to multiple blood pressure medications
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Yes. Improved BP control clearly results in lower mortality, cardiovascular death and cardiovascular events.
10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Taking into account possible future reduction in costs to the healthcare system from end organ complications of poorly controlled hypertension, including RDN in the hypertension pathway has the potential to result in considerable savings for the healthcare system.
11 - MTEP	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	It is likely to cost more to deliver this as part of the care pathway but this initial cost is likely to be offset by the downstream savings to the healthcare system from better blood pressure control
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	No changes to existing facilities

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Yes. Operators with more experience have better outcomes. Each device has specific training and a learning curve to ensure the best outcomes

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Femoral artery complication < 1 in 100, minor and unlikely to extend hospital stay Renal Artery Stenosis < 1 in 1000 (European Heart Journal (2019) 40, 3474–3482)
15	Please list the key efficacy outcomes for this procedure/technology?	Reduction in ambulatory blood pressure 5-10mmHg
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Unclear who will respond to the procedure. Whilst most patients do respond a proportion do not and this is the subject on ongoing research.
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Unclear who will respond to the procedure. Whilst most patients do respond a proportion do not and this is the subject on ongoing research. The effect seems to improve over time - unclear why.
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	A minority of hospitals, but at least 10 in the UK. At least initially so that outcomes and efficacy can be mapped. Clinical trials of RDN have shown reduced benefit in low volume centres.

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Mahfoud F, Kandzari DE, Kario K, et al. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. Lancet. 2022;Epub ahead of print.
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	GSR DEFINE registry – Medtronic, global registry

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Depends on group which we are targeting. Treatment resistant hypertension (excluding non - compliant patients) would suggest 10-15% of hypertension patients (British Journal of General Practice 2018; 68 (671): e394-e400. **DOI:** https://doi.org/10.3399/bjgp18X696221)
22	Are there any issues with the usability or practical aspects of the procedure/technology?	Learning curve for operator, otherwise very straightforward
23	Are you aware of any issues which would prevent (or have prevented) this	no

	procedure/technology being adopted in your organisation or across the wider NHS?	
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Identifying patients who are unlikely to respond. Currently the focus of research
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: – Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. – Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured:	Beneficial outcome measures: 1. >5mmHg reduction in ABPM 2. Incidence of stroke 3. Incidence of admission for hypertension crisis 4. Incidence of renal failure 5. Incidence of myocardial infarction 6. Incidence of heart failure. Above should be documented at 1 year, then monitored annually for 5 years Adverse outcome measures: 1. Femoral complication rate 2. Renal artery stenosis

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	The field has learnt from a premature and rapid adoption of this technology approximately 10 years ago. Its clear that RDN is more efficacious in appropriately trained units with sufficient volume. The governance of the hypertension pathway also needs to be very clear. The patients should be discussed in an MDT forum prior to any procedure to ensure all medical avenues have been explored prior to a denervation.

NICE National Institute for Health and Care Excellence

Declarations of interests

Please state any potential conflicts of interest relevant to the procedure/technology (or competitor technologies) on which you are providing advice, or any involvements in disputes or complaints, in the previous **12 months** or likely to exist in the future. Please use the NICE policy on declaring and managing interests as a guide when declaring any interests. Further advice can be obtained from the NICE team.

Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Choose an item.			
Choose an item.			
Choose an item.			

X I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during the course of my work with NICE, must be notified to NICE as soon as practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate and timely declarations then my advice may be excluded from being considered by the NICE committee.

Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**Dr Sayan Sen**
Dated:	**14/04/22**

NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: IP923/2 Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension

Your information

Name:	Professor Indranil Dasgupta
Job title:	Consultant Nephrologist, Honorary Professor of Nephrology and Hypertension
Organisation:	University Hospital Birmingham and University of Warwick
Email address:	[redacted]
Professional organisation or society membership/affiliation:	UK Kidney Association, European Renal Association, International Society of Nephrology, British and Irish Hypertension Society
Nominated/ratified by (if applicable):	NA
Registration number (e.g. GMC, NMC, HCPC)	4177773

How NICE will use this information: the advice and views given in this questionnaire will form part of the information used by NICE and its advisory committees to develop guidance or a medtech innovation briefing on this procedure/technology. Information may be disclosed to third parties in accordance with the Freedom of Information Act 2000 and the Data Protection Act 2018, complying with data sharing guidance issued by the Information Commissioner's Office. Your advice and views represent your individual opinion and not that of your employer, professional society or a consensus view. Your name, job title, organisation and your responses, along with your declared interests will also be published online on the NICE website as part of the process of public consultation on the draft guidance, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.

For more information about how we process your data please see our privacy notice.

☒ I give my consent for the information in this questionnaire to be used and may be published on the NICE website as outlined above. If consent is NOT given, please state reasons below:

Click here to enter text.

Please answer the following questions as fully as possible to provide further information about the procedure/technology and/or your experience.

Please note that questions 10 and 11 are applicable to the Medical Technologies Evaluation Programme (MTEP). We are requesting you to complete these sections as future guidance may also be produced under their work programme.

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology?	I established the first renal denervation service in Midlands in 2012. We carried out over 40 procedures for treatment resistant hypertension, between 2012 and 2014, until a moratorium was placed on the procedure in the UK. However, we continued to perform the procedure within a research study until 2016. We also introduced renal denervation using carbon dioxide renal angiography in people with CKD to reduce the contrast load, which, I believe, is a first in the world. We reported our own experience and the collective experience in the UK (of 253 procedures) of renal denervation. Altogether, I have published 11 articles on this procedure in peer reviewed journals and presented widely in national and international conferences. I am the co-author of the 2 consensus statements published on behalf of the joint UK societies including the Renal Association which I represented.
	Have you used it or are you currently using it? – Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? – Is this procedure/technology performed/used by clinicians in specialities other than your own? – If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please	The procedure is not currently being used in the UK because of the moratorium on its use outside research studies. To my knowledge there are at least 18 centres in the UK that have the expertise and previous experience of using the technology. Therefore, it can be adopted very quickly in the NHS. Yes, cardiologists, interventional radiologists and clinical pharmacologists Yes, both as hypertension specialists working up and referring patients for procedure and also in

	indicate your experience with it.	helping to select patients, in particular those with CKD, for other specialities
2	− Please indicate your research experience relating to this procedure (please choose one or more if relevant):	I have done bibliographic research on this procedure. • Renal sympathetic denervation for treatment of hypertension: where are we now in 2019? Dasgupta I, Sharp ASP. Curr Opin Nephrol Hypertens. 2019 Sep;28(5):498-506. doi: 10.1097/MNH.0000000000000532. • Renal Denervation. Hameed MA, Dasgupta I. Adv Exp Med Biol. 2017;956:261-277. doi: 10.1007/5584_2016_148. I have done research on this procedure in laboratory settings (e.g. device-related research). • Phase II randomized sham-controlled study of renal denervation for individuals with uncontrolled hypertension - WAVE IV. Schmieder RE, Ott C, Toennes SW, Bramlage P, Gertner M, Dawood O, Baumgart P, O'Brien B, Dasgupta I, et al. J Hypertens. 2018 Mar;36(3):680-689. doi: 10.1097/HJH.0000000000001584. • The use of carbon dioxide angiography for renal sympathetic denervation: a technical report. Renton M, Hameed MA, Dasgupta I, Hoey ET, Freedman J, Ganeshan A. Br J Radiol. 2016 Dec;89(1068):20160311. doi: 10.1259/bjr.20160311. I have done clinical research on this procedure involving patients and I have published this research: • Renal denervation using carbon dioxide renal angiography in patients with uncontrolled hypertension and moderate to severe chronic kidney disease. Hameed MA, Freedman JS, Watkin R, Ganeshan A, Dasgupta I. Clin Kidney J. 2017 Dec;10(6):778-782. doi: 10.1093/ckj/sfx066. Epub 2017 Aug 29. • Phase II randomized sham-controlled study of renal denervation for individuals with uncontrolled hypertension - WAVE IV. Schmieder RE, Ott C, Toennes SW, Bramlage P, Gertner M, Dawood O, Baumgart P, O'Brien B, Dasgupta I, Nickenig G, Ormiston J, Saxena M, Sharp ASP, Sievert H, Spinar J, Starek Z, Weil J, Wenzel U, Witkowski A, Lobo MD. • J Hypertens. 2018 Mar;36(3):680-689. doi: 10.1097/HJH.0000000000001584. The use of carbon dioxide angiography for renal sympathetic denervation: a technical report. Renton M, Hameed MA, Dasgupta I, Hoey ET, Freedman J, Ganeshan A. Br J Radiol. 2016 Dec;89(1068):20160311. doi: 10.1259/bjr.20160311. • Renal artery sympathetic denervation: observations from the UK experience. Sharp AS, Davies JE, Lobo MD, … Dasgupta I. Clin Res Cardiol. 2016 Jun;105(6):544-52. doi: 10.1007/s00392-015-0959-4. • Renal Denervation in Patients With Uncontrolled Hypertension and Confirmed Adherence to Antihypertensive Medications. Hameed MA, Pucci M, Martin U, Watkin R, Doshi S, Freedman J, Riley P, Townend J, Crowe P, Lipkin G, Dasgupta I. J Clin Hypertens (Greenwich). 2016 Jun;18(6):565-71. doi: 10.1111/jch.12713. • First report of the Global SYMPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled hypertension. Böhm M, Mahfoud F, Ukena C, et al; GSR Investigators. Hypertension. 2015 Apr;65(4):766-74. 10.1161/HYPERTENSIONAHA.114.05010. • Renal sympathetic denervation for resistant hypertension: a transiently sustained placebo effect? Purvis TE, Shipman KE, Watkin R, Freedman J, Crowe P, Dasgupta I. J Hum Hypertens. 2015 Jun;29(6):396-7. doi: 10.1038/jhh.2014.102.

		Other (please comment) – co-authored two consensus statements: • Joint UK societies' 2019 consensus statement on renal denervation. Lobo MD, Sharp ASP, Kapil V, Davies J, de Belder MA, Cleveland T, Bent C, Chapman N, Dasgupta I, et al; British & Irish Hypertension Society, the British Cardiovascular Society, the British Cardiovascular Intervention Society, the British Society of Interventional Radiology and the Renal Association. Heart. 2019 Oct;105(19):1456-1463. doi: 10.1136/heartjnl-2019-315098. • Joint UK societies' 2014 consensus statement on renal denervation for resistant hypertension. Lobo MD, de Belder MA, Cleveland T, Collier D, Dasgupta I, et al; British Hypertension Society; British Cardiovascular Society; British Cardiovascular Intervention Society; Renal Association. Heart. 2015 Jan;101(1):10-6. doi: 10.1136/heartjnl-2014-307029.
3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Since it was first introduced in clinical practice in the UK in 2011, the technology has evolved significantly to address many of the lessons learnt from the design and conduct of the first sham-controlled trial (SYMPLICITY HTN-3) published in 2014. The current multi-electrode radiofrequency catheters with different technical properties are able to deliver simultaneous four quadrant radio-frequency ablations in a retrograde spiral in a shorter time of energy delivery. Use of these catheters enable more complete denervation. Three sham-controlled trials using the new technology has demonstrated significant BP lowering in the intervention arm. ~~Established practice and no longer new.~~ A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. *The variation has improved the procedure's safety and efficacy significantly.* ~~Definitely novel and of uncertain safety and efficacy.~~ ~~The first in a new class of procedure.~~
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Yes, certainly as described below

Current management

5	Please describe the current standard of care that is used in the NHS.	The current standard of care in the NHS is to add further classes of antihypertensive drugs to existing medication with no/ very little improvement in BP control. Furthermore, 50% of treatment resistant hypertensives are non-adherent to medications, and a significant number suffer from multiple antihypertensive drug intolerance.
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	There is no competing technology available to the NHS. An endovascular ultra-sound based renal denervation technology (Radio-sound) is currently being trialled in the UK and elsewhere. The proofs of principle study results of this technology are encouraging.

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Improvement in BP control and consequent reduction in CV events, CKD/ ESKD, hospitalisation and mortality. Two proof of principle trials (SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED) and one pivotal trial (SPYRAL HTN-OFF MED Pivotal Trial) have shown impressive benefit in BP control (around 6 mmHg difference in mean ambulatory systolic BP between the groups). The durability of this effect has been demonstrated in the recently published pre-specified post-hoc analysis of the SPYRAL HTN-ON MED trial. At 36 months, the ambulatory systolic blood pressure reduction was −18·7 mm Hg (SD 12·4) for the renal denervation group (n=30) and −8·6 mm Hg (14·6) for the sham control group (n=32; adjusted treatment difference −10·0 mm Hg, 95% CI −16·6 to −3·3; p=0·0039). There were no short or long-term safety issues. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00455-X/fulltext
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	1. **Treatment resistant hypertensives (TRH)** Prevalence is around 5-10% of all adult hypertensive patients. They have at least 50% higher risk of cardiovascular events and mortality compared to those with controlled resistant hypertension. A 10-mmHg reduction in office systolic BP, similar to that observed in SPYRAL ON MED trial, is likely to be associated with 17% lower relative risk of coronary artery disease, 27% lower relative risk of stroke, 28% lower relative risk of heart failure and 13% lower relative risk of mortality. Therefore, the degree of average BP reduction observed in the recent RDN trials could translate into significant benefit to patients with treatment-resistant hypertension. 2. **Non-adherent to antihypertensive medication** Up to 50% of treatment resistant hypertensives are either partially, or completely, non-adherent to prescribed medications. The underlying reasons are complex. **3. Intolerant to multiple antihypertensive agents** **4. Young hypertensive individuals reluctant to take medication or unable fit into their busy working life** All of these groups of individuals have higher risks of cardiovascular events, chronic kidney disease and mortality; as such, they are also candidates for device-based treatments for hypertension. Even the highest standards of anti-hypertensive care have shown non-adherence remains a problem and that RDN can help in this scenario.

	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Yes, certainly. For the patient groups mentioned above, in particular those with TRH, it will potentially change the management pathway leading to improved BP control and consequent reduction in CV events, ESKD, hospitalisation and mortality.
10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Considering the potential reduction in cardio-vascular complications of hypertension, outpatient visits and hospitalisation, cost of wasted antihypertensive medications (£100 million by DoH report in 2010), cost of renal replacement therapy (£30K per patient per year), etc. this procedure is likely lead to considerable saving to the NHS. This I feel will be substantiated by health economic analysis.
11 - MTEP	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	There is upfront cost for the renal denervation catheters which is likely to be offset by long-term saving in medication cost, reduced hospital visits, costs of treating complications Space in interventional radiology or cardiology labs Trained personnel - 18 NHS Trust already have experienced staff, it is considered to be an easy procedure to learn by experienced interventional radiologists and cardiologists It is a day-case procedure
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	The procedure can be done in any interventional radiology or cardiology lab without any adaptation
13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	As mentioned before, it is considered to be an easy procedure to learn by experienced interventional radiologists and cardiologists. For the uninitiated, proctoring is required for the first couple of procedures which can be provided by experienced personnel from a nearby Trust.

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Very few adverse events have been reported in the renal denervation studies performed this far, both with the old and new technologies. The recently published post-hoc analysis of SPYRAL HTN-ON MED trial did not find any short or long-term safety issues. Local pain and bleeding post-procedure – minor issue in our experience Contrast induced acute kidney injury in those with CKD – uncommon, generally transient Vascular embolism – rare, anecdotal Renal artery perforation – rare, anecdotal Renal artery dissection – rare, anecdotal Renal artery stenosis long-term – very rare, anecdotal
15	Please list the key efficacy outcomes for this procedure/technology?	Reduction in mean ambulatory BP Reduction in number of antihypertensive medications Safety profile – short and long-term Clinical predictors of response to the intervention Hard outcome data from long-term studies and registries
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	In our own experience and that in various trials, not all patients have similar BP lowering response to the procedure. Therefore, it is very important to identify clinical predictors of response so that this invasive procedure can be applied to those who are likely to benefit most.
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	The current technology is safe and efficacious in the short and medium term. Large long-term studies are required to support long-term safety and durability of efficacy, although the recently published post-hoc analysis of SPYRAL-ON MED addresses this to an extent. Long-term registry data will also be important in this respect. Trials are also needed to provide long-term hard outcome data.
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please	Most or all district general hospitals.

	choose one):	~~A minority of hospitals, but at least 10 in the UK.~~ ~~Fewer than 10 specialist centres in the UK.~~ ~~Cannot predict at present.~~

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Mahfoud F, Kandzari DE, Kario K, Townsend RR, Weber MA, Schmieder RE, Tsioufis K, Pocock S, Dimitriadis K, Choi JW, East C, D'Souza R, Sharp ASP, Ewen S, Walton A, Hopper I, Brar S, McKenna P, Fahy M, Böhm M. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. Lancet. 2022 Apr 9;399(10333):1401-1410. doi: 10.1016/S0140-6736(22)00455-X. Epub 2022 Apr 4. PMID: 35390320. Yang X, Liu H, Chen S, Dong P, Zhao D. Intravascular Renal Denervation Reduces Ambulatory and Office Blood Pressure in Patients with Essential Hypertension: A Meta-Analysis of Randomized Sham-Controlled Trials. Kidney Blood Press Res. 2022 Apr 6. doi: 10.1159/000524171. Dasgupta I, Sharp ASP. Renal sympathetic denervation for treatment of hypertension: where are we now in 2019? Curr Opin Nephrol Hypertens. 2019 Sep;28(5):498-506. doi: 10.1097/MNH.0000000000000532. PMID: 31268917. Renal artery sympathetic denervation: observations from the UK experience. Sharp AS, Davies JE, Lobo MD, Bent CL, Mark PB, Burchell AE, Thackray SD, Martin U, McKane WS, Gerber RT, Wilkinson JR, Antonios TF, Doulton TW, Patterson T, Clifford PC, Lindsay A, Houston GJ, Freedman J, Das N, Belli AM, Faris M, Cleveland TJ, Nightingale AK, Hameed A, Mahadevan K, Finegold JA, Mather AN, Levy T, D'Souza R, Riley P, Moss JG, Di Mario C, Redwood SR, Baumbach A, Caulfield MJ, Dasgupta I. Clin Res Cardiol. 2016 Jun;105(6):544-52. doi: 10.1007/s00392-015-0959-4.
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Global Symplicity Registry Study SPYRAL HTN-ON MED PIVOTAL Trial https://clinicaltrials.gov/ct2/show/NCT02439775

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Difficult to estimate but around 5% of adult hypertensive patients have true treatment resistant hypertension. Around 31% of men and 26% of women have hypertension in the UK. The current adult population of the UK is 67.1 million. Therefore, a significant number of people with hypertension in the UK are likely to be eligible for the procedure each year.
22	Are there any issues with the usability or practical aspects of the procedure/technology?	No
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	No, except funding and lifting of the moratorium
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Larger trials with true treatment resistant hypertensives, i.e. uncontrolled hypertension despite treatment with 3 or more antihypertensive agents used in optimum doses, replicating the results of OFF MED and ON MED trials will be useful
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late	Beneficial outcome measures: Change in average daytime/ 24-hour ambulatory systolic BP – at 6 months Number (%) achieving BP target by standardised office BP measurement at 6 months and then yearly Number (%) achieving BP target by home BP monitoring using the BIHS guidance at 6 months and then yearly QoL measures Hospital attendance and in-patient episodes for CV events Adverse outcome measures: Local pain, discomfort, bleeding post-procedure and at 1 month

	complications. Please state the post procedure timescales over which these should be measured:	Renal artery injury post procedure Vascular events post procedure Renal artery stenosis at 36 months although this is rare and it may not be feasible to scan every patients at 24 to 36 months to look for this complication

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Management of treatment resistant hypertension is challenging. The currently available 4th, 5th, 6th … line antihypertensive agents are not effective in controlling BP in these patients. On the other hand, these are often associated with significant side effects. TRH is associated with at least 50% higher risk of CV events, ESKD, hospitalisations and mortality compared with controlled hypertension. This has significant human, societal and health service costs. Device based therapy, like renal denervation, has the potential to improve BP control and clinical outcomes in TRH patients. The initial enthusiasm of renal denervation for TRH was dampened by the results of the SUMPLICITY HTN 3 trial, which we now know had a number of design and procedural flaws accounting for negative results. This led to the moratorium on its use in the UK. However, our analysis of all renal denervation procedures done in the UK (n=253) until 2014 demonstrated significant benefit in terms of BP lowering in true TRH. We believe this was because of meticulous patient selection and correct performance of the procedure in the UK. Recent trials, using the second-generation renal denervation catheters and addressing the design and procedural issues of SYMPLICITY HTN 3 trial, have shown impressive BP reduction compared with sham procedure in both treatment naïve and on-treatment hypertensive patients. A recent post-hoc analysis of ON MED trial has demonstrated long-term safety and durability of benefit of the procedure. These encouraging results raise the possibility of using the technology for the treatment of TRH in clinical practice in the near future.

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Declarations of interests

Please state any potential conflicts of interest relevant to the procedure/technology (or competitor technologies) on which you are providing advice, or any involvements in disputes or complaints, in the previous **12 months** or likely to exist in the future. Please use the NICE policy on declaring and managing interests as a guide when declaring any interests. Further advice can be obtained from the NICE team.

Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Choose an item.	None		
Choose an item.			
Choose an item.			

☒ I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during the course of my work with NICE, must be notified to NICE as soon as practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate and timely declarations then my advice may be excluded from being considered by the NICE committee.

Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**Click here to enter text.Indranil Dasgupta**
Dated:	**Click here to enter text.12/04/2022**

NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: **IP923/2 Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension**

Your information

Name:	PROFESSOR MELVIN D LOBO
Job title:	DIRECTOR BARTS BP CLINIC, CONSULTANT IN CV MEDICINE
Organisation:	BARTS HEALTH NHS TRUST
Email address:	[redacted]
Professional organisation or society membership/affiliation:	BIHS, FACC, FESC, FRCP
Nominated/ratified by (if applicable):	N/A
Registration number (e.g. GMC, NMC, HCPC)	GMC: 3325506

How NICE will use this information: the advice and views given in this questionnaire will form part of the information used by NICE and its advisory committees to develop guidance or a medtech innovation briefing on this procedure/technology. Information may be disclosed to third parties in accordance with the Freedom of Information Act 2000 and the Data Protection Act 2018, complying with data sharing guidance issued by the Information Commissioner's Office. Your advice and views represent your individual opinion and not that of your employer, professional society or a consensus view. Your name, job title, organisation and your responses, along with your declared interests will also be published online on the NICE website as part of the process of public consultation on the draft guidance, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.

For more information about how we process your data please see our privacy notice.

☒ I give my consent for the information in this questionnaire to be used and may be published on the NICE website as outlined above. If consent is NOT given, please state reasons below:

Please answer the following questions as fully as possible to provide further information about the procedure/technology and/or your experience.

Please note that questions 10 and 11 are applicable to the Medical Technologies Evaluation Programme (MTEP). We are requesting you to complete these sections as future guidance may also be produced under their work programme.

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology?	I am familiar with this technology having been an investigator/steering committee member of numerous multicentre randomised controlled trials using radiofrequency/ultrasound/chemical renal sympathetic denervation. I also chair the Joint UK Societies Working Group on Renal Denervation (RDN).
	Have you used it or are you currently using it? – Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake?	Our current moratorium (PMID: 31292190) reserves use of RDN for patients in clinical trials and thus the procedure is not being used in the NHS outside of this scope.
	– Is this procedure/technology performed/used by clinicians in specialities other than your own?	I am unaware of clinicians using the procedure outside of interventional cardiology/radiology/hypertension and then only within clinical trials
	– If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	My specialty is involved in patient selection (Hypertension Specialist) and we have MDT meetings with interventional cardiology/radiology to select patients for the clinical trials enrolment. We have treated more than 100 patients in randomised clinical trials with the different modalities mentioned above: the procedure is safe and appears to be effective in ~70% of patients

2	– Please indicate your research experience relating to this procedure (please choose one or more if relevant):	I have done bibliographic research on this procedure. I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research
3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	This is an innovative approach which should be considered for patients with both systolic & diastolic hypertension whose BP is not controlled with conventional lifestyle and drug therapy approaches and who need improved BP control due to high risk of CV events. Importantly it gets arounds issues of non-adherence to antihypertensive medication which is a major obstacle to hypertension control globally. Also it could be offered to those patients who are intolerant of antihypertensive medications The first in a new class of procedure: this technology has been iterated over the past decade and recent clinical trials published in Lancet have demonstrated safety and efficacy to 3 years
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	It would be an addition to existing standard of care

Current management

5	Please describe the current standard of care that is used in the NHS.	Lifestyle modification and drug therapy of hypertension as per NICE guidance

6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	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. The database for US renal denervation also demonstrates safety and efficacy in medicated and non-medicated patients. Ethnol mediated ablation is earlier in its trajectory but on the same path as the other two modalities and may turn out to be superior for BP reduction.

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Improved BP control during day and night with reduced burden of anti-hypertensive medications. In some patients there may the possibility of not requiring antihypertensive medications at all.
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Any patient who does not have a secondary form of hypertension who cannot achieve hypertension control with lifestyle modification and drug therapy. It may be appropriate to target those at highest CV risk given the invasive nature of the procedure with high costs.
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Yes – it could conceivably reduce need for follow up visits for drug titrations/drug surveillance. We all recognise that reducing BP lowers CV outcomes – an outcome trial will not be possible with this technology but up to 10 mm Hg of ambulatory BP lowering should translate into reduced CV morbidity & mortality.
10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Up-front costs will be higher as drug therapy now very cheap but this will be offset by reduction in follow up visits for BP control and in all likelihood reduction in stroke/coronary syndromes due to improved BP control.

11 - MTEP	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	There will be significant resource impact as this will cost more than standard care and will require cath lab staff & time
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Multidisciplinary team with hypertension specialists & interventionists working together. Interventional catheterisation laboratory
13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Yes – this is provided by the manufacturers by way of proctoring

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Renovascular damage is possible but occurs very rarely. Groin site complications as per any other cath lab procedure As above None that are device/procedure related (PMID: 35390320) None other than goring site complications Theoretical: Renovascular disorder, impaired renal function
15	Please list the key efficacy outcomes for this procedure/technology?	Systolic BP reduction using ABPM and office measurement

16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Long term durability not established. It is probably less effective in the setting of isolated systolic hypertension
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Role of RDN in hypertension care pathway not determined – who should get it and when? We are unable to predict responders/non-responders to the therapy at present
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	A minority of hospitals, but at least 10 in the UK.

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Cost effectiveness data is now due to be presented but has not been published: both Medtronic and ReCor Medical have demonstrated that the technology is cost effective according to UK standards. A cost effectiveness dataset from ReCor Medical has just been accepted for publication in Blood Pressure journal. Patient preference data (Patient Preferences For Interventional And Pharmaceutical Treatments Among US Adults With Uncontrolled Hypertension *Michael Weber, Atul Pathak, Christine Poulos, Sidney A. Cohen, Joshua Coulter, Denise Jones, David Kandzari,) presented at TCT 2021*

20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	There are 31 active clinical trials of renal denervation presently: https://www.clinicaltrials.gov/ct2/results?cond=&term=renal+denervation&type=&rslt=&recrs=a&recrs=d&age_v=&age=1&age=2&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	This depends entirely on the population selected for treatment and could be some/all patients with resistant hypertension whose BP cannot be controlled in expert hands as well as some patients with multidrug intolerant hypertension
22	Are there any issues with the usability or practical aspects of the procedure/technology?	None that I am aware of
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	No – prior evaluation was done at a time when there was insufficient evidence to support the clinical adoption (in 2014). The recent clinical trials demonstrate that the technology is now ready for clinical use.
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Further information is desirable on predictors of response and procedural efficacy but this may take time to develop and should not hold back use of the technology to treat hypertension Registries will provide long term safety data – Medtronic & ReCor Medical are committed to this
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: – Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement	Beneficial outcome measures: BP reduction – Ambulatory BP, home BP and clinic BP Medication burden reduction Improvement in QoL (EQ5D) MACE at 6 months, annually after Procedural details

	for each and the timescales over which these should be measured. – Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured:	Renal function should be monitored 1,6,12 months post procedure and annually after Renovascular disorder screened for 1 year post treatment

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Patient preference studies indicate that patients are willing to accept the risk of the RDN procedure to achieve hypertension control and are very keen to avoid lifelong polypharmacy where possible. The therapy is cost effective and this will be published in 2022

NICE National Institute for Health and Care Excellence

Declarations of interests

Please state any potential conflicts of interest relevant to the procedure/technology (or competitor technologies) on which you are providing advice, or any involvements in disputes or complaints, in the previous **12 months** or likely to exist in the future. Please use the NICE policy on declaring and managing interests as a guide when declaring any interests. Further advice can be obtained from the NICE team.

Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Direct - financial	Consultant to Medtronic, ReCor Medical and Ablative Solutions who all manufacture RDN technologies	**Since 2015**	**ongoing**
Direct - financial	I have received educational grants from Medtronic & ReCor Medical	**2019**	**ongoing**
Choose an item.			

☒ I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during the course of my work with NICE, must be notified to NICE as soon as practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate and timely declarations then my advice may be excluded from being considered by the NICE committee.

Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**Click here to enter text.Melvin D LOBO**
Dated:	**Click here to enter text.11.04.2022**