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Efficacy and Safety of Renal Denervation for Chinese Patients with Resistant Hypertension Using a Micro-irrigated Catheter: Study Design and Protocol for a Prospective Multicenter Randomized Controlled Trial

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5 2 Resistant Hypertension Using a Micro-irrigated Catheter: Study Design and
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7 3 Protocol for a Prospective Multicenter Randomized Controlled Trial
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40 40 Short title: Renal denervation for Chinese patients with resistant hypertension
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3 **42 Abstract:**

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6 **43 Introduction:** Available data show that approximately 8-18% of patients with primary
7 hypertension will develop resistant hypertension. In recent years, catheter-based renal
8 denervation (RDN) has emerged as a potential treatment option for resistant hypertension.
9 A number of observational studies and randomized controlled trials among non-Chinese
10 patients have demonstrated its potential safety and efficacy.
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15 **48 Methods and Analysis:** This is a multicenter, randomized, open-label, parallel-group,
16 active controlled trial that will investigate the efficacy and safety of a 5F saline-irrigated
17 radiofrequency ablation (RFA) catheter used for RDN in the treatment of Chinese
18 patients with resistant hypertension. A total of 254 patients who have failed
19 pharmacological therapy will be enrolled. Eligible subjects will be randomized in a 1:1
20 ratio to undergo RDN using the RFA catheter plus antihypertensive medication, or to
21 receive treatment with antihypertensive medication alone. The primary outcome measure
22 is the change in 24-hour ambulatory systolic blood pressure from baseline to 3 months,
23 comparing the RDN-plus-medication group with the medication-alone group. Important
24 secondary endpoints include the change in office blood pressure from baseline to 6
25 months after randomization. Safety endpoints will also be evaluated. The full analysis set,
26 according to the intent-to-treat principle, will be established as the primary analysis
27 population.
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38 **61 Conclusion:** This study is designed to investigate the efficacy and safety of RDN using a
39 5F saline micro-irrigated RFA catheter in Chinese patients with hypertension who are
40 resistant to medication. It aims to provide clinical evidence that RDN with the RFA
41 catheter is both safe and effective in Chinese patients. (Words: 248)
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46 **65 Trial registration:** [ClinicalTrials.gov ID: NCT02900729](https://clinicaltrials.gov/ct2/show/study/NCT02900729)

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49 **66 Key words:** resistant hypertension, renal denervation, radiofrequency ablation catheter,
50 ambulatory blood pressure, Chinese patients
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53 **68 Abbreviations:** RDN, renal denervation; RFA, radiofrequency ablation
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3 70 **Strengths and limitations of this study**
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- 6 71 ● A micro-irrigated catheter used for renal denervation;
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8 72 ● A randomized controlled trial accords in principle with recommendations by
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10 European Expert Group;
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13 74 ● Enroll Chinese hypertensive patients only, which might affect generability of study
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15 findings
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79 Introduction

80 Hypertension represents a significant global public health problem, contributing to
81 vascular and renal morbidity, cardiovascular mortality, and economic burden. Although
82 there are many methods for treating primary hypertension, more than half of the patients
83 are still unable to achieve their treatment goal^{1, 2}. Available data show that 8-18% of
84 patients will develop resistant hypertension^{3, 4}, defined as a systolic blood pressure (SBP)
85 of 140mmHg or higher despite adherence to at least three maximally tolerated doses of
86 antihypertensive medications from complementary classes, including a diuretic at an
87 appropriate dose⁵. Compared with those with controlled blood pressure (BP), patients
88 with resistant hypertension are at greater risk for developing adverse cardiovascular
89 events, leading to an unfavorable prognosis without adequate treatment⁶. Because of the
90 complex pathophysiology of resistant hypertension, however, there are limited strategies
91 available to treat it efficiently.

92 Following the clinical use of radiofrequency ablation (RFA) catheters in recent years,
93 catheter-based renal denervation (RDN) has emerged as a potential treatment option for
94 resistant hypertension. This technique delivers low-level radiofrequency energy
95 throughout the renal artery wall to disrupt renal nerves and thereby modulate BP to some
96 extent. A number of observational studies and randomized controlled trials among non-
97 Chinese patients have demonstrated both the safety and the potential efficacy of this new
98 therapy⁷⁻¹⁵, whereas several other studies failed to show extra benefits when RDN was
99 applied¹⁶⁻¹⁸. Whenever doubts arise concerning the effectiveness of a therapeutic
100 approach, rigorously designed studies are warranted to furnish conclusive evidence.
101 According to the clinical consensus from the European Expert Group¹⁹, many factors
102 could affect the results of RDN in clinical trials, including procedural aspects, patient
103 populations, and design considerations. Many aspects of the RDN procedure may affect
104 the success of the ablation; furthermore, whether denervation has been completely
105 achieved in a specific patient remains the key factor for the efficacy of RDN.

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3 107 Together with these key recommendations¹⁹, we present the rationale and methodology
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5 108 for a randomized, controlled trial of RDN using a 5F saline micro-irrigated RFA catheter
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7 109 for the treatment of hypertension in Chinese patients who have failed standardized
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9 110 pharmacologic therapy.

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12 112 **Methods/design**

13 113 **Study design**

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18 114 This trial ([ClinicalTrials.gov ID: NCT02900729](https://clinicaltrials.gov/ct2/show/study/NCT02900729)) is a multicenter, randomized, open-label,
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20 115 parallel-group, active controlled trial that will investigate the efficacy and safety of a 5F
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22 116 saline-irrigated RFA catheter used in RDN for the treatment of Chinese patients with
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24 117 resistant hypertension. It will be conducted in accordance with the principles outlined in
25
26 118 the Declaration of Helsinki and will follow the Consolidated Standards of Reporting
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28 119 Trials (CONSORT) statement (<http://www.consort-statement.org/>). Approximately 13
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30 120 clinical centers will participate in this trial, which has been approved by the Independent
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32 121 Ethics Committee for each site. All subjects will be required to sign a written informed
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34 122 consent document before their participation in the trial. A brief flow chart of this trial is
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36 123 provided in [Figure 1](#).

37 124 **Study patients**

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39 125 A total of 254 patients who have failed pharmacological therapy will be enrolled. The
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41 126 following are the inclusion criteria:

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43 127 1. Subject with primary hypertension has 24-hour ambulatory SBP \geq 135 mmHg and
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45 128 office SBP \geq 140 mmHg /office diastolic blood pressure (DBP) \geq 90 mmHg after
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47 129 4weeks' standardized triple therapy.
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49 130 2. Subject is \geq 18 and $<$ 80 years old at the time of randomization.
- 50
51 131 3. Subject agrees to have all study procedures performed, and is willing to provide
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53 132 written informed consent to participate in this clinical study.

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55 133 The exclusion criteria are as follows:

- 134 1. Subject has acute or serious systemic infection.
- 135 2. Subject has a history of renal artery interventional therapy.
- 136 3. Subject lacks suitable renal artery anatomy for percutaneous renal sympathetic nerve
137 RFA surgery, including but not limited to the presence of serious aorta or renal-
138 artery tortuosity or renal-artery stenosis.
- 139 4. Subject has experienced a myocardial infarction, unstable angina pectoris, syncope,
140 or a cerebrovascular accident within three months of the screening period, or has
141 widespread atherosclerosis, with documented intravascular thrombosis.
- 142 5. Subject has aortic dissection aneurysm.
- 143 6. Subject has primary pulmonary hypertension.
- 144 7. Subject has an estimated glomerular filtration rate of less than 40 mL/min/1.73m²
145 according to the Modification of Diet in Renal Disease formula.
- 146 8. Subject had a definite diagnose of coronary heart disease requiring beta-blockers
- 147 9. Subject has Class III-IV heart failure or left ventricular ejection fraction <45%.
- 148 10. Subject has atrial fibrillation.
- 149 11. Subject has a significant bleeding tendency or blood system disease(s).
- 150 12. Subject has a malignancy or end-stage disease(s).
- 151 13. Subject has secondary hypertension.
- 152 14. Subject has type 1 diabetes mellitus.
- 153 15. Subject has other conditions inappropriate for participation, at the investigator's
154 discretion.
- 155 16. Subject has a medical ethics issue of concern, at the investigator's discretion, such as
156 presence of an average SBP \geq 170 mmHg on 24-hour ambulatory BP monitoring after
157 4weeks'standardized triple therapy.

158 **Recruitment process**

159 Before enrollment, there will be two screening visits. Each participant will be assigned a
160 unique identification number during the first screening visit. In addition to the above
161 mentioned entry criteria, patients with primary hypertension who meet any of the three
162 following criteria will be considered for further evaluation at the second screening visit:

- 163 ● Adherence to 3 kinds of antihypertensive medication, office SBP ≥ 140 mmHg or
164 office DBP ≥ 90 mmHg, and office SBP < 180 mmHg, office DBP < 100 mmHg.
- 165 ● Adherence to two kinds of antihypertensive medication, office SBP ≥ 140 mmHg, or
166 office DBP ≥ 90 mmHg.
- 167 ● Adherence to one kind of antihypertensive medication, office SBP ≥ 160 mmHg, or
168 office DBP ≥ 100 mmHg.

169 For any initially eligible patients as mentioned above, three basic kinds of
170 antihypertensive medication, e.g. standardized triple antihypertensive medications
171 consisting of amlodipine 5mg per day, losartan potassium 50mg, and hydrochlorothiazide
172 12.5mg per day, will be administered for at least 4 weeks (run-in period). Patients who
173 meet the following BP threshold criteria will then be eligible for randomized assignment
174 after the second screening period: 24h ambulatory BP ≥ 135 mmHg and office SBP
175 ≥ 140 mmHg, or office DBP ≥ 90 mmHg.

176 **Randomization process**

177 Eligible patients with resistant hypertension will be randomly assigned to one of two
178 study treatment groups in a 1:1 ratio. A stratified block randomization with randomly
179 varying block size will be performed, stratified according to study site. Random
180 assignment is generated by an independent statistician and implemented via random
181 envelopes assigned to each site. In order to avoid potential selection bias, the sequence is
182 concealed from both clinical staff and patients until assignment. Hence, neither
183 investigators nor participants can influence which group the study patients are assigned to.

184 **Description of the interventions**

185 The enrolled subjects will be randomized to undergo RDN using a 5F saline micro-
186 irrigated RFA catheter plus antihypertensive medication, or to be treated with
187 antihypertensive medication alone. RDN will be performed according to the device's
188 instructions for use.

189 The study patients will be advised to maintain baseline antihypertensive medication in the
190 first 90 days after randomization. However, the three baseline antihypertensive

191 medications (e.g. calcium antagonist, angiotensin II receptor antagonist, diuretics) will be
192 adjusted after randomization when clinically necessary. Criterion for dosage reduction:
193 subjects experience a sudden reduction in BP within a short time, meanwhile
194 accompanied by ischemic symptoms (weakness, dizziness, syncope, fall, etc.). If these
195 symptoms disappear and 72-hour average home SBP is ≥ 140 mmHg or DBP ≥ 90 mmHg,
196 the antihypertensive medication may be restored to the original type and dosage.
197 Criterion for dosage increase: if home SBP is ≥ 170 mmHg for an observational period of
198 72 hours from randomization through 90 days, or from 91 days through 180 days if
199 average home SBP is ≥ 140 mmHg or DBP is ≥ 90 mmHg based on three consecutive daily
200 measurements, the following three kinds of drugs could be added, one per month in
201 sequence: aldactone 20mg per day, metoprolol succinate sustained-release tablet 47.5mg
202 per day, and clonidine hydrochloride tablets 75ug t.i.d (Figure 1).

203 For patients receiving antihypertensive medication alone, after maintenance of baseline
204 standardized triple antihypertensive medications for 90 days post randomization and then
205 medically necessary adjustment of antihypertensive medications for another 90 days,
206 subjects will be allowed to cross over to undergo RDN if they still meet the original
207 inclusion criteria for the study.

208 **Renal denervation procedure**

209 Under local anesthesia, RDN procedures are to be performed by interventionists at each
210 study site after a unified training session. Following preoperative preparation, the
211 ablation catheter will be advanced to the distal segment of the renal artery through the 7F
212 guidance catheter.

213 The ablation involves at least six applications to each renal artery, according to the length
214 of the artery's main stem. If the main renal artery is less than 15 mm, two ablations
215 should be delivered to the main bifurcation with diameter >3 mm in order to ensure six
216 ablation lesions on each side. Treatment begins from the distal end of the artery or the
217 main bifurcation in a helical pattern as the catheter is pulled back.

218 For every renal artery ostium, the catheter must be maneuvered to at least one position in
219 each of the distal, middle and proximal segments. The ablation energy will be 8-10 W in

220 the distal segment, 10-11 W in the middle segment and 12 W in the proximal segment.
221 Each ablation will last 60s. The ideal target outcome is for the energy titration to achieve
222 a 10% to 20% drop in impedance at each location. If the drop in impedance is less than
223 5%, or the ablation energy is unable to achieve the preset wattage, the ablation will be
224 stopped and the catheter will be repositioned.

225 **Study visits**

226 Nine study visits will be scheduled following the baseline visit: once every 15 days in the
227 first 90 days and then every 30 days until 180 days. For the 3rd, 5th, 7th, and 10th visits
228 patients will return to the clinic office; for the remaining visits, the patients will be
229 consulted by phone. At every visit, data relating to BP, medication, adverse events, etc.,
230 will be collected.

231 The subjects may withdraw from the study if any of the following conditions occur:

- 232 ● After 4 weeks post randomization, the office or home SBP is ≥ 180 mmHg for more
233 than one week while standardized antihypertensive medications are maintained.
- 234 ● Based on the investigator's discretion, the subject is no longer eligible for the study
235 for any reason.

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237 **Outcome measures**

238 **Primary outcome**

239 The primary outcome of this study is the change in 24-hour ambulatory SBP from
240 baseline to 3 months compared between the RDN-plus-medication group and the
241 medication-only group. This outcome will be strictly standardized in terms of uniform
242 validated devices, appropriate cuff, identical clinical setting, and resting condition prior
243 to BP measurement after mandatory one-day stay in participating site, etc.

244 **Secondary outcomes**

- 245 1. Change in office systolic/diastolic BP from baseline to 6 months post-
246 randomization.
- 247 2. Incidence of achieving target BP at 6 months post-randomization. Target BP is
248 defined as daytime ambulatory BP <135/85mmHg, nighttime ambulatory BP
249 <120/70mmHg, or average 24-hour ambulatory BP <130/80mmHg.
- 250 3. Incidence of substantially adjusting antihypertensive medications at 6 months
251 post-randomization. A substantial adjustment of antihypertensive medications is
252 defined as any change in the number or type of antihypertensive medications, or a
253 $\geq 50\%$ dose change in the last two weeks with respect to any ongoing
254 antihypertensive medications.
- 255 4. Incidence of achieving reductions of ≥ 5 mmHg, ≥ 10 mmHg, ≥ 15 mmHg, and ≥ 20
256 mmHg in BP, including ambulatory, office, and home BP at 6 months post-
257 randomization.

258 Safety endpoints

259 The safety endpoints mainly include any adverse events, a change in renal function
260 (serum creatinine, urea nitrogen, serum uric acid, etc.), other laboratory tests (liver
261 function, serum biochemistry), and cardiovascular complications.

262 Sample size calculation

263 We used R V.3.2.3 (R Core Team. R: A language and environment for statistical
264 computing. Vienna, Austria: R Foundation for Statistical Computing,
265 2014.<http://www.R-project.org/>; last accessed June 2016) to estimate sample size. The
266 trial is designed to compare the difference in average ambulatory SBP as a change from
267 baseline to 3 months between the RDN-plus-medication group and the medication-alone
268 group. With a sample size of 108 randomized patients per group, the between-group
269 comparison will be powered at 90% to establish the superiority of added RDN for the
270 primary endpoint at a two-sided significance level of 0.05, assuming that the true SBP
271 difference is 8mmHg with a common standard deviation of 18mmHg. Given an expected
272 dropout rate of 15% in the first 3 months post randomization, a total of 254 patients (127
273 patients per group) must be enrolled in the study.

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3 274 Results of 10,000 simulations using this estimated sample size for each study showed that
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5 275 an empirical power of 98% would be reached for the analysis of the BP target rate (56%
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7 276 versus 44%) as the important efficacy endpoint, using the Cochran-Mantel-Haenszel
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9 277 (CMH) test with antihypertensive medication adjusted or not within the last 2 weeks as
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11 278 stratification factor.

12 13 279 **Statistical analysis**

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15 280 The full analysis set, according to the intent-to-treat principle, will be established as the
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17 281 primary analysis population. A two-sided p-value of <0.05 will be considered to indicate
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19 282 significance for any statistical tests. R, V.3.2.3 and SAS software, V.9.2 (SAS Institute,
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21 283 North Carolina, USA) will be used for statistical analysis. Such data as demographics,
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23 284 baseline characteristics, and safety will be summarized according to treatment group.

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25 285 The primary efficacy outcomes will be analyzed using analysis of covariance (ANCOVA)
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27 286 with treatment group as fixed factor and BP values at baseline as covariate. The paired
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29 287 and unpaired t-tests will further be used to test BP reduction within each group and
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31 288 between groups, respectively. The 95% confidence intervals for the differences between
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33 289 treatment groups will also be calculated. Subgroup analyses are prespecified according to
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35 290 the following prognostic factors: sex, age, diabetes, body mass index, estimated
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37 291 glomerular filtration rate, and aldosterone use at baseline.

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39 292 Blood pressure target rate at 6 months will be analyzed using the CMH test, with
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41 293 antihypertensive medication adjusted or not within the last 2 weeks as stratification factor.

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43 294 Other categorical data will be tested using Pearson's chi-square test or Fisher's exact test,
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45 295 as appropriate. Other continuous efficacy endpoints will be analyzed similarly to the
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47 296 primary endpoint. Mixed-model repeated measures analysis including terms for treatment
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49 297 group, time, baseline measurement, and time by treatment group interaction will be
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51 298 considered to compare BP reduction in the study.

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54 55 300 **Discussion**

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3 301 The design and methods of this trial satisfy the requirements to test whether a 5F saline
4 302 micro-irrigated RFA catheter used in RDN is safe and effective for patients who remain
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6 303 hypertensive despite adherence to polypharmacy.
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9 304 With the recognition of the role of the sympathetic nervous system in the development
10 305 and progression of hypertension^{20, 21}, catheter-based RDN has been developed to reduce
11 306 sympathetic nervous activity and subsequently reduce BP, as well as morbidity and
12 307 mortality, in patients with uncontrolled hypertension²²⁻²⁵. However, the clinical evidence
13 308 in support of RDN as an effective interventional technique in patients with resistant
14 309 hypertension appears conflicting. Several large studies support both the safety and the
15 310 efficacy of this new therapy⁷⁻¹⁵, but some smaller studies failed to show the superiority
16 311 resulting from added RDN¹⁶⁻¹⁸. In view of this controversy, the European Expert Group
17 312 convened a clinical consensus conference and agreed on recommendations for future
18 313 randomized controlled trials of RDN in hypertension. The design and methods of our trial
19 314 accord in principle with the recommendations.
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29 315 The RDN procedure is so complex that the efficacy of ablation may be influenced by
30 316 many factors, such as renal artery anatomy, the depth of the ablation lesion,
31 317 atherosclerosis, etc. Achieving complete ablation will pose a challenge to the operator,
32 318 the equipment, and the procedure. A study of the anatomic assessment of sympathetic
33 319 peri-arterial renal nerves showed that the greatest number of nerves were observed in the
34 320 proximal and middle segments of the renal artery, while the smallest number were seen in
35 321 the distal segment. However, in the main renal artery, the distance from the nerve to the
36 322 renal artery lumen is shorter than in the proximal and middle segments, being
37 323 approximately 4.28mm²⁶. Another study showed that, for a patient with atherosclerosis,
38 324 the RFA-induced damage did not penetrate deeper than 2mm from the luminal surface,
39 325 leaving unaffected a large part of the nerves in (peri-) adventitial areas remote from the
40 326 vascular lumen²⁷. An animal study showed that the ablation zone geometries varied in arc,
41 327 area, and depth, depending on the composition of the adjacent tissue substructure²⁸. In
42 328 addition, the delivered power density was influenced by tissue substructure, and peaked
43 329 at the conductivity discontinuities between soft fatty adventitia and water-rich tissues, not
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3 330 at the electrode-tissue interface²⁸. With a greater recognition of nerve distribution, the
4 331 ablation depth and location should be taken carefully into account.

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7 332 In previous studies, a non-irrigated catheter was usually used and the ablation energy was
8 333 usually 8W. Increasing ablation energy or prolonging ablation time could make the
9 334 ablation deeper. However, using a non-irrigated catheter could raise the temperature of
10 335 the luminal surface too much to increase the ablation power. In this study, radiofrequency
11 336 energy delivery with the use of cold saline irrigation seems safe and effective. By
12 337 actively cooling the ablation electrode during RFA, it is possible to minimize the
13 338 possibility of char formation and also decrease the probability of vasospasm. These
14 339 advantages to saline irrigation are so significant that most cardiac ablations are now
15 340 performed using irrigated ablation catheters²⁹. Ahmed et al., in a small single-arm study,
16 341 demonstrated that RDN can be performed safely and effectively using a saline-irrigated
17 342 RFA catheter in patients with hypertension³⁰. Using a saline-irrigated catheter, with the
18 343 protection of cold saline, higher ablation energy can be delivered, ensuring the ablation
19 344 depth. Indeed, the saline-irrigated catheter has been widely used in cardiac ablation.

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23 345 In most clinical trials involving RDN, a renal artery less than 4mm in diameter could not
24 346 be ablated because of the limited operation equipment. In this study, the 5F saline micro-
25 347 irrigated RFA catheter is smaller and more flexible, so it can be used in renal arteries
26 348 with diameter <4mm, while minimizing the possibility of peripheral artery-related
27 349 complications.

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31 350 In this study, the operation procedure will also be unified. A similar spiral ablation will
32 351 be used and at least one site must be ablated at each of the distal segments of the renal
33 352 artery, the middle segment, proximal, and opening. Four quadrants will be ablated. There
34 353 are a total of 6 ablation points on each side of the renal artery. The ablation energy will
35 354 also be standardized to ensure sufficient ablation.

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40 355 In this trial, patients with 24-hour ambulatory SBP ≥ 135 mmHg and office SBP
41 356 <170mmHg will be eligible for enrollment, while patients with high-risk characteristics
42 357 will be excluded. Given this restriction, the patients enrolled in this study will mostly
43 358 have mild to moderate hypertension and might be more responsive to RDN-induced

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3 359 changes in sympathetic tone. In addition, it will be safer for these patients to strictly
4 360 follow a standardized medication regimen. Moreover, higher drug adherence will be
5 361 expected in this study, because of the lower level of discomfort occurring in the
6 362 management of mild to moderate rather than severe hypertension.

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11 363 In the study period, the antihypertensive medications administered are explicitly specified:
12 364 standardized triple antihypertensive medications include a calcium channel blocker, a
13 365 renin-angiotensin system blocker, and a diuretic. In the Symplicity HTN-3 study¹⁶, the
14 366 maximum doses were administered, and 39% patients required medication adjustment
15 367 because of adverse events; this may be related to the negative conclusions of that study.
16 368 Conversely, in the DENERHTN study¹⁵, the antihypertensive medications in the RDN
17 369 group and control group were strictly regulated, and the study results supported the
18 370 superiority of RDN. The rigorous specification of medication may be an important factor
19 371 influencing the study results.

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27 372 For this study, ambulatory BP is used as the primary endpoint, and office BP as the
28 373 secondary parameter. In fact, several previous studies have documented a better
29 374 prognostic value of ambulatory over office BP in different populations³¹⁻³⁵. Among the
30 375 previous trials conducted on RDN, only the DENERHTN study¹⁵ successfully used the
31 376 change in mean daytime ambulatory SBP as primary endpoint, and that study found RDN
32 377 to have superior efficacy. The Expert Group also strongly recommended ambulatory BP
33 378 as the primary measure of response to RDN. Using ambulatory BP monitoring to measure
34 379 efficacy could exclude pseudo-resistance due to a “white-coat” effect.

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42 380 There is also one limitation regarding the selection of the control group. Because of the
43 381 poor acceptability by patients in our routine clinical practice and potential ethical
44 382 problems, a sham operation will not be performed in this study; its omission might thus
45 383 be a potential confounder for study outcomes. Although a sham procedure could reduce
46 384 some Hawthorne effects, it could not eliminate other biases that are considered as reasons
47 385 for the lack of benefit from RDN.

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53 386 This study is designed to investigate the efficacy and safety of RDN using a 5F saline-
54 387 irrigated RFA catheter in Chinese patients with hypertension who are resistant to

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3 388 medication therapy. Its goal is to provide clinical evidence that RDN with a 5F saline-
4 389 irrigated RFA catheter is both safe and effective in Chinese patients with drug-resistant,
5 390 systemic hypertension.
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10 11 392 **Trial status**

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14 393 The study is not yet recruiting as of the date of submission.
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16 17 394 **Competing interests**

18
19 395 None.
20

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23
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28 29 399 **Contributors**

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31 400 ZJL, LS and JBG conceived and designed the study. ZJL, LS and SZ supervised the
32 401 power analyses and wrote the data analysis section. ZJL and JBG bear overall
33 402 responsibility for the design, ethical conduct and publication of the study. Administrative,
34 403 technical and material support was provided by ZJL and LS. All authors involved the
35 404 protocol discussion and they will take responsibility for study data gathering and
36 405 verification. All authors edited the draft and contributed substantially to the manuscript;
37 406 they all approved this submission.
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45
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50 51 52 410 **References** 53 54 55 56 57 58 59 60

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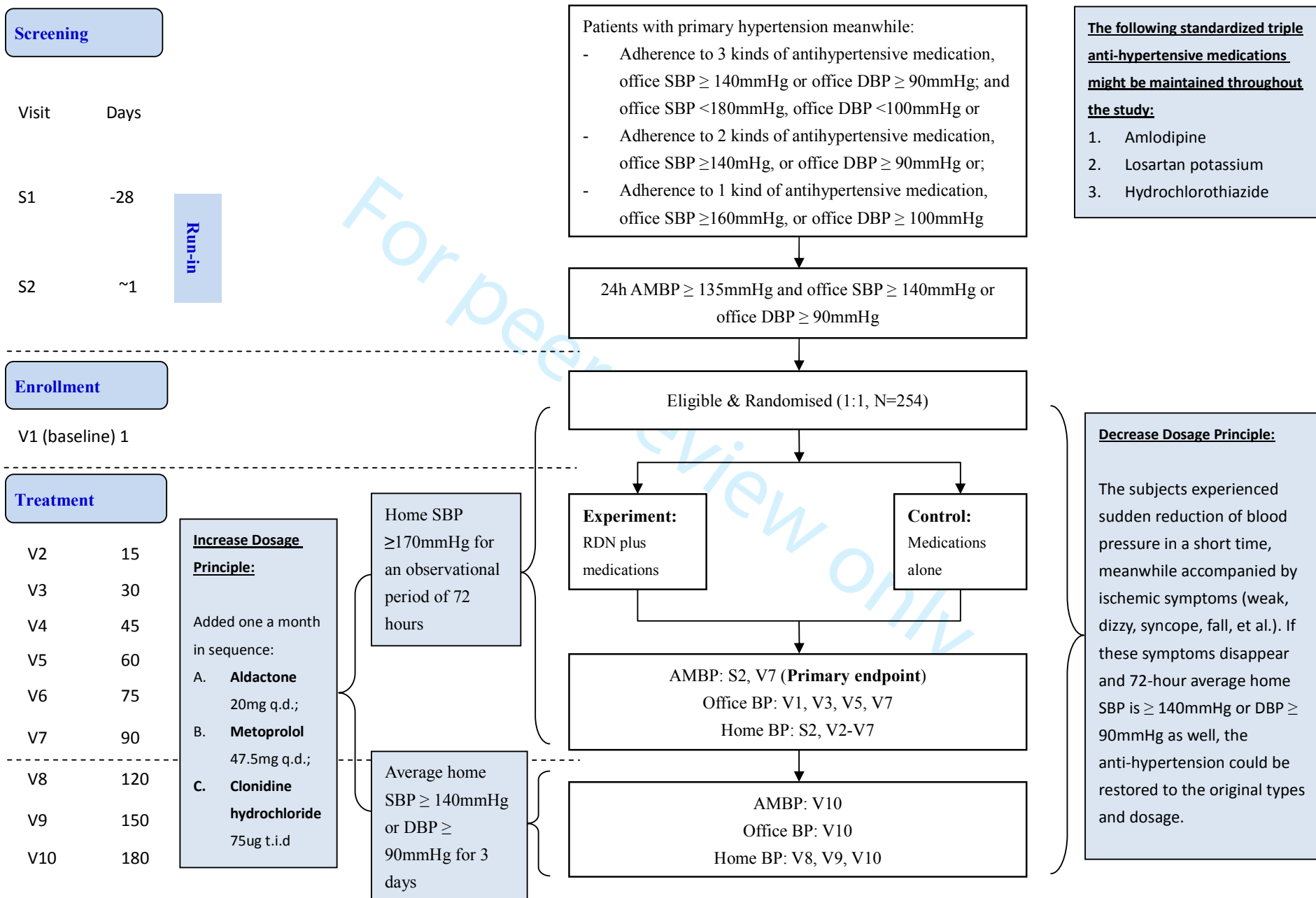
512 [Figure 1](#): Study flowchart and principles of adjusting antihypertensive medications

513 Abbreviations: ABPM: Ambulatory Blood Pressure Monitoring; BP: Blood Pressure;

514 DBP: Diastolic Blood Pressure; RDN: Renal Denervation; SBP: Systolic Blood Pressure

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SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p.3
	2b	All items from the World Health Organization Trial Registration Data Set	n.a.
Protocol version	3	Date and version identifier	n.a.
Funding	4	Sources and types of financial, material, and other support	p.16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p.1, 2, 16
	5b	Name and contact information for the trial sponsor	p.1, 2, 16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n.a.
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n.a.
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p.5, 6
	6b	Explanation for choice of comparators	p.5, 6

Section/item	Item No	Description	Addressed on page number
Objectives	7	Specific objectives or hypotheses	p.6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p.6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p.6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p.6, 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p. 8,9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p. 9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	p.8, 9, 10, figure 1
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	p.8, 9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p.10, 11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see fig 1[f1])	figure 1

Section/item	Item No	Description	Addressed on page number
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p.11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n. a.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers) and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p.8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p.8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p.8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts) and how	p.8
	17b	If blinded, circumstances under which unblinding is permissible and procedure for revealing a participant's allocated intervention during the trial	p.8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if	Figure 1

Section/item	Item No	Description	Addressed on page number
		not in the protocol	
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n.a.
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	n.a.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p.12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p.12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p.12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n.a.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n.a.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n.a.
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators	n.a.

Section/item	Item No	Description	Addressed on page number
		and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p.6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n.a.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p.6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n.a.
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p.16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n.a.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	n.a.

Section/item	Item No	Description	Addressed on page number
	31b	Authorship eligibility guidelines and any intended use of professional writers	p.16
	31c	Plans, if any, for granting public access to the full protocol, participant level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n.a.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.

BMJ Open

Efficacy and Safety of Renal Denervation for Chinese Patients with Resistant Hypertension Using a Micro-irrigated Catheter: Study Design and Protocol for a Prospective Multicenter Randomized Controlled Trial

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	resistant hypertension, renal denervation, radiofrequency ablation catheter, ambulatory blood pressure, Chinese patients

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SCHOLARONE™
Manuscripts

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1 Efficacy and Safety of Renal Denervation for Chinese Patients with
2 Resistant Hypertension Using a Micro-irrigated Catheter: Study Design and
3 Protocol for a Prospective Multicenter Randomized Controlled Trial
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5 Zongjun Liu^{1,*}, Li Shen^{2,*}, Weijian Huang³, Xianxian Zhao⁴, Weiyi Fang⁵, Changqian Wang⁶, Zhaofang
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39 39 *These authors contributed equally to this work.

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42 40 Short title: Renal denervation for Chinese patients with resistant hypertension

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42 **Abstract:**

43 **Introduction:** Available data show that approximately 8-18% of patients with primary
44 hypertension will develop resistant hypertension. In recent years, catheter-based renal
45 denervation (RDN) has emerged as a potential treatment option for resistant hypertension.
46 A number of observational studies and randomized controlled trials among non-Chinese
47 patients have demonstrated its potential safety and efficacy.

48 **Methods and Analysis:** This is a multicenter, randomized, open-label, parallel-group,
49 active controlled trial that will investigate the efficacy and safety of a 5F saline-irrigated
50 radiofrequency ablation (RFA) used for RDN in the treatment of Chinese patients with
51 resistant hypertension. A total of 254 patients who have failed pharmacological therapy
52 will be enrolled. Eligible subjects will be randomized in a 1:1 ratio to undergo RDN
53 using the RFA catheter plus antihypertensive medication, or to receive treatment with
54 antihypertensive medication alone. The primary outcome measure is the change in 24-
55 hour ambulatory systolic blood pressure from baseline to 3 months, comparing the RDN-
56 plus-medication group with the medication-alone group. Important secondary endpoints
57 include the change in office blood pressure from baseline to 6 months after
58 randomization. Safety endpoints such as changes in renal function will also be evaluated.
59 The full analysis set, according to the intent-to-treat principle, will be established as the
60 primary analysis population.

61 **Ethics and Dissemination:** All participants will provide informed consent; the study
62 protocol has been approved by the Independent Ethics Committee for each site. This
63 study is designed to investigate the efficacy and safety of RDN using a 5F saline micro-
64 irrigated RFA catheter. Findings will be shared with participating hospitals, policymakers
65 and the academic community to promote the clinical management of resistant
66 hypertension in China. (Words: 267)

67 **Trial registration:** [ClinicalTrials.gov ID: NCT02900729](https://clinicaltrials.gov/ct2/show/study/NCT02900729)

68 **Key words:** resistant hypertension, renal denervation, radiofrequency ablation catheter,
69 ambulatory blood pressure, Chinese patients

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70 **Abbreviations:** RDN, renal denervation; RFA, radiofrequency ablation

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72 **Strengths and limitations of this study**

- 73 ● A randomized controlled trial accords in principle with recommendations by
74 European Expert Group;
- 75 ● Strict standardization of anti-hypertensive medications during the study;
- 76 ● Enroll Chinese hypertensive patients only, which might affect generability of study
77 findings
- 78 ● Failure to implement sham procedure as control might introduce Hawthorne effects.

82 Introduction

83 Hypertension represents a significant global public health problem, contributing to
84 vascular and renal morbidity, cardiovascular mortality, and economic burden. Although
85 there are many methods for treating primary hypertension, more than half of the patients
86 are still unable to achieve their treatment goal^{1,2}. Available data show that approximately
87 8-18% of patients with primary hypertension present with resistant hypertension^{3, 4},
88 defined as a systolic blood pressure (SBP) of 140mmHg or higher despite adherence to at
89 least three maximally tolerated doses of antihypertensive medications from
90 complementary classes, including a diuretic at an appropriate dose⁵. Compared with those
91 with controlled blood pressure (BP), patients with resistant hypertension are at greater
92 risk for developing adverse cardiovascular events, leading to an unfavorable prognosis
93 without adequate treatment⁶. Because of the complex pathophysiology of resistant
94 hypertension, however, there are limited strategies available to treat it efficiently.

95 Following the clinical use of radiofrequency ablation (RFA) catheters in recent years,
96 catheter-based renal denervation (RDN) has emerged as a potential treatment option for
97 resistant hypertension. This technique delivers low-level radiofrequency energy
98 throughout the renal artery wall to disrupt renal nerves and thereby modulate BP to some
99 extent. A number of observational studies and randomized controlled trials among non-
100 Chinese patients have demonstrated both the safety and the potential efficacy of this new
101 therapy⁷⁻¹⁵, whereas several other studies failed to show extra benefits when RDN was
102 applied¹⁶⁻¹⁸. Whenever doubts arise concerning the effectiveness of a therapeutic
103 approach, rigorously designed studies are warranted to furnish conclusive evidence.
104 According to the clinical consensus from the European Expert Group¹⁹, many factors
105 could affect the results of RDN in clinical trials, including procedural aspects, patient
106 populations, and design considerations. Many aspects of the RDN procedure may affect
107 the success of the ablation; furthermore, whether denervation has been completely
108 achieved in a specific patient remains the key factor for the efficacy of RDN.

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3 110 Together with these key recommendations¹⁹, we present the rationale and methodology
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5 111 for a randomized, controlled trial of RDN using a 5F saline micro-irrigated RFA catheter
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7 112 for the treatment of hypertension in Chinese patients who have failed standardized
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9 113 pharmacologic therapy.

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14 115 **Methods/design**

16 116 **Study design**

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19 117 This trial ([ClinicalTrials.gov ID: NCT02900729](https://clinicaltrials.gov/ct2/show/study/NCT02900729)) is a multicenter, randomized, open-label,
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21 118 parallel-group, active controlled trial that will investigate the efficacy and safety of a 5F
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23 119 saline-irrigated RFA catheter used in RDN for the treatment of Chinese patients with
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25 120 resistant hypertension. The RFA catheter under study is manufactured by Shanghai
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27 121 WiseGain Medical Devices Co., Ltd. Approximately 13 clinical centers will participate in
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29 122 this trial. A brief flow chart of this trial is provided in [Figure 1](#).

30 123 **Study patients**

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33 124 A total of 254 patients who have failed pharmacological therapy will be enrolled. The
34
35 125 following are the inclusion criteria:

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38 126 1. Subject with primary hypertension has 24-hour ambulatory SBP \geq 135 mmHg and
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40 127 office SBP \geq 140 mmHg /office diastolic blood pressure (DBP) \geq 90 mmHg after
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42 128 4weeks' standardized triple therapy.
- 43 129 2. Subject is \geq 18 and $<$ 80 years old at the time of randomization.
- 44
45 130 3. Subject agrees to have all study procedures performed, and is willing to provide
46
47 131 written informed consent to participate in this clinical study.

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49 132 The exclusion criteria are as follows:

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52 133 1. Subject has acute or serious systemic infection.
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54 134 2. Subject has a history of renal artery interventional therapy.
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- 135 3. Subject lacks suitable renal artery anatomy for percutaneous renal sympathetic nerve
- 136 RFA surgery, including but not limited to the presence of serious aorta or renal-
- 137 artery tortuosity or renal-artery stenosis.
- 138 4. Subject has experienced a myocardial infarction, unstable angina pectoris, syncope,
- 139 or a cerebrovascular accident within three months of the screening period, or has
- 140 widespread atherosclerosis, with documented intravascular thrombosis.
- 141 5. Subject has aortic dissection aneurysm.
- 142 6. Subject has primary pulmonary hypertension.
- 143 7. Subject has an estimated glomerular filtration rate of less than 40 mL/min/1.73m²
- 144 according to the Modification of Diet in Renal Disease formula.
- 145 8. Subject had a definite diagnose of coronary heart disease requiring beta-blockers
- 146 9. Subject has Class III-IV heart failure or left ventricular ejection fraction <45%.
- 147 10. Subject has atrial fibrillation.
- 148 11. Subject has a significant bleeding tendency or blood system disease(s).
- 149 12. Subject has a malignancy or end-stage disease(s).
- 150 13. Subject has secondary hypertension.
- 151 14. Subject has type 1 diabetes mellitus.
- 152 15. Subject has other conditions inappropriate for participation, at the investigator's
- 153 discretion.
- 154 16. Subject has a medical ethics issue of concern, at the investigator's discretion, such as
- 155 presence of an average SBP \geq 170 mmHg on 24-hour ambulatory BP monitoring after
- 156 4weeks'standardized triple therapy.

157 **Recruitment process**

158 Before enrollment, there will be two screening visits. Each participant will be assigned a
159 unique identification number during the first screening visit. In addition to the above-
160 mentioned entry criteria, patients with primary hypertension who meet any of the three
161 following criteria will be considered for further evaluation at the second screening visit:

- 162 ● Adherence to 3 kinds of antihypertensive medication, office SBP \geq 140mmHg or
- 163 office DBP \geq 90mmHg, and office SBP <180mmHg, office DBP <100mmHg.

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- 164 ● Adherence to two kinds of antihypertensive medication, office SBP ≥ 140 mmHg, or
 - 165 office DBP ≥ 90 mmHg.
 - 166 ● Adherence to one kind of antihypertensive medication, office SBP ≥ 160 mmHg, or
 - 167 office DBP ≥ 100 mmHg.

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168 For any initially eligible patients as mentioned above, three basic kinds of
169 antihypertensive medication, e.g. standardized triple antihypertensive medications
170 consisting of amlodipine 5mg per day, losartan potassium 50mg, and hydrochlorothiazide
171 12.5mg per day, will be administered for at least 4 weeks (run-in period). Patients who
172 meet the following BP threshold criteria will then be eligible for randomized assignment
173 after the second screening period: 24h ambulatory BP ≥ 135 mmHg and office SBP
174 ≥ 140 mmHg, or office DBP ≥ 90 mmHg.

25 **Randomization process**

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176 Eligible patients with resistant hypertension will be randomly assigned to one of two
177 study treatment groups in a 1:1 ratio. A stratified block randomization with randomly
178 varying block size will be performed, stratified according to study site. Random
179 assignment is generated by an independent statistician and implemented via random
180 envelopes assigned to each site. In order to avoid potential selection bias, the sequence is
181 concealed from both clinical staff and patients until assignment. Hence, neither
182 investigators nor participants can influence which group the study patients are assigned to.

40 **Description of the interventions**

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184 The enrolled subjects will be randomized to undergo RDN using a 5F saline micro-
185 irrigated RFA catheter plus antihypertensive medication, or to be treated with
186 antihypertensive medication alone. RDN will be performed according to the device's
187 instructions for use.

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188 The study patients will be advised to maintain baseline antihypertensive medication in the
189 first 90 days after randomization. However, the three baseline antihypertensive
190 medications (e.g. calcium antagonist, angiotensin II receptor antagonist, diuretics) will be
191 adjusted after randomization when clinically necessary. Criterion for dosage reduction:

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3 192 subjects experience a sudden reduction in BP within a short time, meanwhile
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5 193 accompanied by ischemic symptoms (weakness, dizziness, syncope, fall, etc.). If these
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7 194 symptoms disappear and 72-hour average home SBP is ≥ 140 mmHg or DBP ≥ 90 mmHg,
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9 195 the antihypertensive medication may be restored to the original type and dosage.
10
11 196 Criterion for dosage increase: if home SBP is ≥ 170 mmHg for an observational period of
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13 197 72 hours from randomization through 90 days, or from 91 days through 180 days if
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15 198 average home SBP is ≥ 140 mmHg or DBP is ≥ 90 mmHg based on three consecutive daily
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17 199 measurements, the following three kinds of drugs could be added, one per month in
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19 200 sequence: aldactone 20mg per day, metoprolol succinate sustained-release tablet 47.5mg
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21 201 per day, and clonidine hydrochloride tablets 75ug t.i.d (Figure 1).

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23 202 For patients receiving antihypertensive medication alone, after maintenance of baseline
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25 203 standardized triple antihypertensive medications for 90 days post randomization and then
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27 204 medically necessary adjustment of antihypertensive medications for another 90 days,
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29 205 subjects will be allowed to cross over to undergo RDN if they still meet the original
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31 206 inclusion criteria for the study.

32 207 **Renal denervation procedure**

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34 208 Under local anesthesia, RDN procedures are to be performed by interventionists at each
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36 209 study site after a unified training session. Following preoperative preparation, the
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38 210 ablation catheter will be advanced to the distal segment of the renal artery through the 7F
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40 211 guidance catheter.

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42 212 The ablation involves at least six applications to each renal artery, according to the length
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44 213 of the artery's main stem. If the main renal artery is less than 15 mm, two ablations
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46 214 should be delivered to the main bifurcation with diameter > 3 mm in order to ensure six
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48 215 ablation lesions on each side. Treatment begins from the distal end of the artery or the
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50 216 main bifurcation in a helical pattern as the catheter is pulled back.

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52 217 For every renal artery ostium, the catheter must be maneuvered to at least one position in
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54 218 each of the distal, middle and proximal segments. The ablation energy will be 8-10W in
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56 219 the distal segment, 10-11W in the middle segment and 12W in the proximal segment. Each
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58 220 ablation will last 60s. The ideal target outcome is for the energy titration to achieve a 10%

221 to 20% drop in impedance at each location. If the drop in impedance is less than 5%, or
222 the ablation energy is unable to achieve the preset wattage, the ablation will be stopped
223 and the catheter will be repositioned.

224 **Study visits**

225 Nine study visits will be scheduled following the baseline visit: once every 15 days in the
226 first 90 days and then every 30 days until 180 days. For the 3rd, 5th, 7th, and 10th visits
227 patients will return to the clinic office; for the remaining visits, the patients will be
228 consulted by phone. At every visit, data relating to BP, medication, adverse events, etc.,
229 will be collected. The 8-item Morisky Medication Adherence Scale (MMAS-8) will be
230 provided at 1st, 3rd, 5th, 7th, and 10th visits.

231 The subjects may withdraw from the study if any of the following conditions occur:

- 232 ● After 4 weeks post randomization, the office or home SBP is ≥ 180 mmHg for more
233 than one week while standardized antihypertensive medications are maintained.
- 234 ● Based on the investigator's discretion, the subject is no longer eligible for the study
235 for any reason.

236

237 **Outcome measures**

238 **Primary outcome**

239 The primary outcome of this study is the change in 24-hour ambulatory SBP from
240 baseline to 3 months compared between the RDN-plus-medication group and the
241 medication-only group. The department of laboratory other than the clinical department
242 at each participating site will undertake the ambulatory blood pressure monitoring
243 (ABPM) during the study period. The ABPM machine will record and report ABPM
244 results automatically. This outcome will be strictly standardized in terms of uniform
245 validated devices, appropriate cuff, identical clinical setting, and resting condition prior
246 to BP measurement after mandatory one-day stay in participating site, etc.

247 **Secondary outcomes**

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3 248 1. Change in office systolic/diastolic BP from baseline to 6 months post-
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5 249 randomization.
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7 250 2. Incidence of achieving target BP at 6 months post-randomization. Target BP is
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9 251 defined as daytime ambulatory BP<135/85mmHg, nighttime ambulatory
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11 252 BP<120/70mmHg, or average 24-hour ambulatory BP<130/80mmHg.
- 12
13 253 3. Incidence of substantially adjusting antihypertensive medications at 6 months
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15 254 post-randomization. A substantial adjustment of antihypertensive medications is
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17 255 defined as any change in the number or type of antihypertensive medications, or a
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19 256 $\geq 50\%$ dose change in the last two weeks with respect to any ongoing
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21 257 antihypertensive medications.
- 22
23 258 4. Incidence of achieving reductions of ≥ 5 mmHg, ≥ 10 mmHg, ≥ 15 mmHg, and ≥ 20
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25 259 mmHg in BP, including ambulatory, office, and home BP at 6 months post-
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27 260 randomization.

261 Safety endpoints

262 The safety endpoints mainly include any adverse events (e.g. puncture hematoma,
263 thrombosis, renal artery stenosis and renal artery dissection as adverse event of special
264 interest, etc), a change in renal function (serum creatinine, urea nitrogen, serum uric acid,
265 creatinine clearance, etc.), other laboratory tests (liver function, serum biochemistry), and
266 cardiovascular complications.

267 Sample size calculation

268 We used R V.3.2.3 (R Core Team. R: A language and environment for statistical
269 computing. Vienna, Austria: R Foundation for Statistical Computing,
270 2014.<http://www.R-project.org/>: last accessed June 2016) to estimate sample size. The
271 trial is designed to compare the difference in average ambulatory SBP as a change from
272 baseline to 3 months between the RDN-plus-medication group and the medication-alone
273 group. With a sample size of 108 randomized patients per group, the between-group
274 comparison will be powered at 90% to establish the superiority of added RDN for the
275 primary endpoint at a two-sided significance level of 0.05, assuming that the true SBP
276 difference is 8mmHg with a common standard deviation of 18mmHg. Given an expected

277 dropout rate of 15% in the first 3 months post randomization, a total of 254 patients (127
278 patients per group) must be enrolled in the study.

279 Results of 10,000 simulations using this estimated sample size for each study showed that
280 an empirical power of 98% would be reached for the analysis of the BP target rate (56%
281 versus 44%) as the important efficacy endpoint, using the Cochran-Mantel-Haenszel
282 (CMH) test with antihypertensive medication adjusted or not within the last 2 weeks as
283 stratification factor.

284 **Statistical analysis**

285 The full analysis set, according to the intent-to-treat principle, will be established as the
286 primary analysis population. A two-sided p-value of <0.05 will be considered to indicate
287 significance for any statistical tests. R, V.3.2.3 and SAS software, V.9.2 (SAS Institute,
288 North Carolina, USA) will be used for statistical analysis. Such data as demographics,
289 baseline characteristics, and safety will be summarized according to treatment group.

290 The primary efficacy outcomes will be analyzed using analysis of covariance (ANCOVA)
291 with treatment group as fixed factor and BP values at baseline as covariate. The paired
292 and unpaired t-tests will further be used to test BP reduction within each group and
293 between groups, respectively. The 95% confidence intervals for the differences between
294 treatment groups will also be calculated. Subgroup analyses are prespecified according to
295 the following prognostic factors: sex, age, diabetes, body mass index, estimated
296 glomerular filtration rate, and aldosterone use at baseline.

297 Blood pressure target rate at 6 months will be analyzed using the CMH test, with
298 antihypertensive medication adjusted or not within the last 2 weeks as stratification factor.

299 Other categorical data will be tested using Pearson's chi-square test or Fisher's exact test,
300 as appropriate. Other continuous efficacy endpoints will be analyzed similarly to the
301 primary endpoint. Mixed-model repeated measures analysis including terms for treatment
302 group, time, baseline measurement, and time by treatment group interaction will be
303 considered to compare BP reduction in the study.

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3 305 **Discussion**
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6 306 The design and methods of this trial satisfy the requirements to test whether a 5F saline
7 307 micro-irrigated RFA catheter used in RDN is safe and effective for patients who remain
8 308 hypertensive despite adherence to polypharmacy.

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12 309 With the recognition of the role of the sympathetic nervous system in the development
13 310 and progression of hypertension^{20, 21}, catheter-based RDN has been developed to reduce
14 311 sympathetic nervous activity and subsequently reduce BP, as well as mortality and
15 312 morbidity, in patients with uncontrolled hypertension²²⁻²⁵ and the prevention of
16 313 recurrences of atrial fibrillation²⁶, the improvement of glycemic control²⁷ and the
17 314 mitigation of pulmonary arterial hypertension as well²⁸. However, the clinical evidence in
18 315 support of RDN as an effective interventional technique in patients with resistant
19 316 hypertension appears conflicting. Several large studies support both the safety and the
20 317 efficacy of this new therapy⁷⁻¹⁵, but some studies failed to show the superiority resulting
21 318 from added RDN¹⁶⁻¹⁸. In view of this controversy, the European Expert Group convened
22 319 a clinical consensus conference and agreed on recommendations for future randomized
23 320 controlled trials of RDN in hypertension. The design and methods of our trial accord in
24 321 principle with the recommendations.

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36 322 The RDN procedure is so complex that the efficacy of ablation may be influenced by
37 323 many factors, such as renal artery anatomy, the depth of the ablation lesion,
38 324 atherosclerosis, etc. Achieving complete ablation will pose a challenge to the operator,
39 325 the equipment, and the procedure. A study of the anatomic assessment of sympathetic
40 326 peri-arterial renal nerves showed that the greatest number of nerves were observed in the
41 327 proximal and middle segments of the renal artery, while the smallest number were seen in
42 328 the distal segment. However, in the main renal artery, the distance from the nerve to the
43 329 renal artery lumen is shorter than in the proximal and middle segments, being
44 330 approximately 4.28mm²⁹. Another study showed that, for a patient with atherosclerosis,
45 331 the RFA-induced damage did not penetrate deeper than 2mm from the luminal surface,
46 332 leaving unaffected a large part of the nerves in (peri-) adventitial areas remote from the
47 333 vascular lumen³⁰. An animal study showed that the ablation zone geometries varied in arc,
48 334 area, and depth, depending on the composition of the adjacent tissue substructure³¹. In
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3 335 addition, the delivered power density was influenced by tissue substructure, and peaked
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5 336 at the conductivity discontinuities between soft fatty adventitia and water-rich tissues, not
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7 337 at the electrode-tissue interface³¹. With a greater recognition of nerve distribution, the
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9 338 ablation depth and location should be taken carefully into account.

10
11 339 In previous studies, a non-irrigated catheter was usually used and the ablation energy was
12
13 340 usually 8W. Increasing ablation energy or prolonging ablation time could make the
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15 341 ablation deeper. However, using a non-irrigated catheter could raise the temperature of
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17 342 the luminal surface too much to increase the ablation power. In this study, radiofrequency
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19 343 energy delivery with the use of cold saline irrigation seems safe and effective. By
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21 344 actively cooling the ablation electrode during RFA, it is possible to minimize the
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23 345 possibility of char formation and also decrease the probability of vasospasm. These
24
25 346 advantages to saline irrigation are so significant that most cardiac ablations are now
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27 347 performed using irrigated ablation catheters³². Ahmed et al., in a small single-arm study,
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29 348 demonstrated that RND can be performed safely and effectively using a saline-irrigated
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31 349 RFA catheter in patients with hypertension³³. Using a saline-irrigated catheter, with the
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33 350 protection of cold saline, higher ablation energy can be delivered, ensuring the ablation
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35 351 depth. Indeed, the saline-irrigated catheter has been widely used in cardiac ablation.

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37 352 In most clinical trials involving RDN, adrenal artery less than 4mm in diameter could not
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39 353 be ablated because of the limited operation equipment. In this study, the 5F saline micro-
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41 354 irrigated RFA catheter is smaller and more flexible, so it can be used in renal arteries
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43 355 with diameter <4mm, while minimizing the possibility of peripheral artery-related
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45 356 complications.

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47 357 In this study, the operation procedure will also be unified. A similar spiral ablation will
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49 358 be used and at least one site must be ablated at each of the distal segments of the renal
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51 359 artery, the middle segment, proximal, and opening. Four quadrants will be ablated. There
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53 360 are a total of 6 ablation points on each side of the renal artery. The ablation energy will
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55 361 also be standardized to ensure sufficient ablation.

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57 362 In this trial, patients with 24-hour ambulatory SBP ≥ 135 mmHg and office SBP
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59 363 <170mmHg will be eligible for enrollment, while patients with high-risk characteristics
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3 364 will be excluded. Given this restriction, the patients enrolled in this study will mostly
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5 365 have mild to moderate hypertension and might be more responsive to RDN-induced
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7 366 changes in sympathetic tone. In addition, it will be safer for these patients to strictly
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9 367 follow a standardized medication regimen. Moreover, higher drug adherence will be
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11 368 expected in this study, because of the lower level of discomfort occurring in the
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13 369 management of mild to moderate rather than severe hypertension.

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15 370 In the study period, the antihypertensive medications administered are explicitly specified:
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17 371 standardized triple antihypertensive medications include a calcium channel blocker, a
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19 372 renin-angiotensin system blocker, and a diuretic. In the Symplicity HTN-3 study¹⁶, the
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21 373 maximum doses were administered, and 39% patients required medication adjustment
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23 374 because of adverse events; this may be related to the negative conclusions of that study.
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25 375 Conversely, in the DENERHTN study¹⁵, the antihypertensive medications in the RDN
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27 376 group and control group were strictly regulated, and the study results supported the
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29 377 superiority of RDN. The rigorous specification of medication may be an important factor
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31 378 influencing the study results.

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33 379 For this study, ambulatory BP is used as the primary endpoint, and office BP as the
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35 380 secondary parameter. In fact, several previous studies have documented a better
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37 381 prognostic value of ambulatory over office BP in different populations³⁴⁻³⁸. Among the
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39 382 previous trials conducted on RDN, only the DENERHTN study¹⁵ successfully used the
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41 383 change in mean daytime ambulatory SBP as primary endpoint, and that study found RDN
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43 384 to have superior efficacy. The Expert Group also strongly recommended ambulatory BP
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45 385 as the primary measure of response to RDN. Using ambulatory BP monitoring to measure
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47 386 efficacy could exclude pseudo-resistance due to a “white-coat” effect.

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49 387 There is also one limitation regarding the selection of the control group. Because of the
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51 388 poor acceptability by patients in our routine clinical practice and potential ethical
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53 389 problems, a sham operation will not be performed in this study; its omission might thus
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55 390 be a potential confounder for study outcomes. Although a sham procedure could reduce
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57 391 some Hawthorne effects, it could not eliminate other biases that are considered as reasons
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59 392 for the lack of benefit from RDN.
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3 393 **Ethics and dissemination**
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6 394 This trial will be conducted in accordance with the principles outlined in the Declaration
7 of Helsinki and will follow the Consolidated Standards of Reporting Trials (CONSORT)
8 395 statement (<http://www.consort-statement.org/>). It has been approved by the Independent
9 396 Ethics Committee for each site (Approval No 2016-46). All subjects will be required to
10 397 sign a written informed consent document before their participation in the trial.
11 398

12
13 399 This study is designed to investigate the efficacy and safety of RDN using a 5F saline-
14 irrigated RFA catheter in Chinese patients with hypertension who are resistant to
15 400 medication therapy. Its goal is to provide clinical evidence that RDN with a 5F saline-
16 401 irrigated RFA catheter is both safe and effective in Chinese patients with drug-resistant,
17 402 systemic hypertension. Findings will be shared with participating hospitals, policymakers
18 403 and the academic community to promote the clinical management of resistant
19 404 hypertension in China.
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31 407 **Trial status**
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34 408 The study enrolled the first patient in March 2017 and is expected to finish patient
35 409 enrolment within 1.5 years.
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38 410 **Competing interests**
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40 411 None. All of the authors report receiving no honoraria from the sponsor.
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42
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44

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47

48
49 415 **Contributors**
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51 416 ZJL, LS and JBG conceived and designed the study. ZJL, LS and SZ supervised the
52 417 power analyses and wrote the data analysis section. ZJL and JBG bear overall
53 418 responsibility for the design, ethical conduct and publication of the study. Administrative,
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3 419 technical and material support was provided by ZJL and LS. All authors involved the
4
5 420 protocol discussion and they will take responsibility for study data gathering and
6
7 421 verification. All authors edited the draft and contributed substantially to the manuscript;
8
9 422 they all approved this submission.

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15
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3 541 [Figure 1](#): Study flowchart and principles of adjusting antihypertensive medications
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6 542 Abbreviations: ABPM: Ambulatory Blood Pressure Monitoring; BP: Blood Pressure;
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8 543 DBP: Diastolic Blood Pressure; RDN: Renal Denervation; SBP: Systolic Blood Pressure
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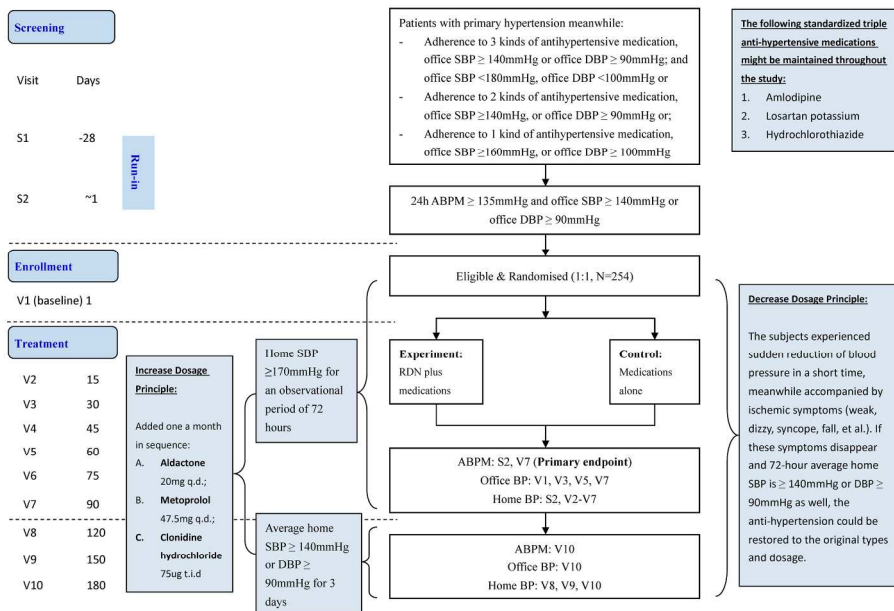


Figure 1: Study flowchart and principles of adjusting antihypertensive medications
 Abbreviations: ABPM: Ambulatory Blood Pressure Monitoring; BP: Blood Pressure; DBP: Diastolic Blood Pressure; RDN: Renal Denervation; SBP: Systolic Blood Pressure

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SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p.3
	2b	All items from the World Health Organization Trial Registration Data Set	n.a.
Protocol version	3	Date and version identifier	n.a.
Funding	4	Sources and types of financial, material, and other support	p.16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p.1, 2, 16
	5b	Name and contact information for the trial sponsor	p.1, 2, 16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	p.21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	p.21
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p.5, 6
	6b	Explanation for choice of comparators	p.5, 6

Section/item	ItemNo	Description	Addressed on page number
Objectives	7	Specific objectives or hypotheses	p.6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p.6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p.6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p.6, 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p.8,9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p. 9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	p.8, 9, 10, figure 1
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	p.8, 9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p.10, 11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants.	figure 1

Section/item	ItemNo	Description	Addressed on page number
		A schematic diagram is highly recommended (see fig 1[f1])	
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p.11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n. a.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers) and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p.8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p.8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p.8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts) and how	p.8
	17b	If blinded, circumstances under which unblinding is permissible and procedure for revealing a participant's allocated intervention during the trial	p.8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires,	Figure 1

Section/item	ItemNo	Description	Addressed on page number
		laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p.18-19
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	n.a.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p.12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p.12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p.12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n.a.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n.a.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p.15

Section/item	ItemNo	Description	Addressed on page number
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n.a.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p.6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n.a.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p.20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p.20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p.16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	p.20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	p.18
Dissemination	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and	p.20

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Section/item	ItemNo	Description	Addressed on page number
policy		other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
	31b	Authorship eligibility guidelines and any intended use of professional writers	p.16
	31c	Plans, if any, for granting public access to the full protocol, participant level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n.a.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.

BMJ Open

Efficacy and Safety of Renal Denervation for Chinese Patients with Resistant Hypertension Using a Micro-irrigated Catheter: Study Design and Protocol for a Prospective Multicenter Randomized Controlled Trial

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	resistant hypertension, renal denervation, radiofrequency ablation catheter, ambulatory blood pressure, Chinese patients

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1 Efficacy and Safety of Renal Denervation for Chinese Patients with
2 Resistant Hypertension Using a Micro-irrigated Catheter: Study Design and
3 Protocol for a Prospective Multicenter Randomized Controlled Trial
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39 39 *These authors contributed equally to this work.

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42 40 Short title: Renal denervation for Chinese patients with resistant hypertension

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42 **Abstract:**

43 **Introduction:** Available data show that approximately 8-18% of patients with primary
44 hypertension will develop resistant hypertension. In recent years, catheter-based renal
45 denervation (RDN) has emerged as a potential treatment option for resistant hypertension.
46 A number of observational studies and randomized controlled trials among non-Chinese
47 patients have demonstrated its potential safety and efficacy.

48 **Methods and Analysis:** This is a multicenter, randomized, open-label, parallel-group,
49 active controlled trial that will investigate the efficacy and safety of a 5F saline-irrigated
50 radiofrequency ablation (RFA) used for RDN in the treatment of Chinese patients with
51 resistant hypertension. A total of 254 patients who have failed pharmacological therapy
52 will be enrolled. Eligible subjects will be randomized in a 1:1 ratio to undergo RDN
53 using the RFA plus antihypertensive medication, or to receive treatment with
54 antihypertensive medication alone. The primary outcome measure is the change in 24-
55 hour average ambulatory systolic blood pressure from baseline to 3 months, comparing
56 the RDN-plus-medication group with the medication-alone group. Important secondary
57 endpoints include the change in office blood pressure from baseline to 6 months after
58 randomization. Safety endpoints such as changes in renal function will also be evaluated.
59 The full analysis set, according to the intent-to-treat principle, will be established as the
60 primary analysis population.

61 **Ethics and Dissemination:** All participants will provide informed consent; the study
62 protocol has been approved by the Independent Ethics Committee for each site. This
63 study is designed to investigate the efficacy and safety of RDN using a 5F saline micro-
64 irrigated RFA. Findings will be shared with participating hospitals, policymakers and the
65 academic community to promote the clinical management of resistant hypertension in
66 China. (Words: 268)

67 **Trial registration:** [ClinicalTrials.gov ID: NCT02900729](https://clinicaltrials.gov/ct2/show/study/NCT02900729)

68 **Key words:** resistant hypertension, renal denervation, radiofrequency ablation,
69 ambulatory blood pressure, Chinese patients

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70 **Abbreviations:** RDN, renal denervation; RFA, radiofrequency ablation

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72 **Strengths and limitations of this study**

- 73 ● A randomized controlled trial accords in principle with recommendations by
74 European Expert Group;
- 75 ● Strict standardization of anti-hypertensive medications during the study;
- 76 ● Enroll Chinese hypertensive patients only, which might affect generability of study
77 findings
- 78 ● Failure to implement sham procedure as control might introduce Hawthorne effects.

82 Introduction

83 Hypertension represents a significant global public health problem, contributing to
84 vascular and renal morbidity, cardiovascular mortality, and economic burden. Although
85 there are many methods for treating primary hypertension, more than half of the patients
86 are still unable to achieve their treatment goal^{1,2}. Available data show that approximately
87 8-18% of patients with primary hypertension present with resistant hypertension^{3,4},
88 defined as a systolic blood pressure (SBP) of 140 mmHg or higher despite adherence to
89 at least three maximally tolerated doses of antihypertensive medications from
90 complementary classes, including a diuretic at an appropriate dose⁵. Compared with those
91 with controlled blood pressure (BP), patients with resistant hypertension are at greater
92 risk for developing adverse cardiovascular events, leading to an unfavorable prognosis
93 without adequate treatment⁶. Because of the complex pathophysiology of resistant
94 hypertension, however, there are limited strategies available to treat it efficiently.

95 Following the clinical use of radiofrequency ablation (RFA) catheters in recent years,
96 catheter-based renal denervation (RDN) has emerged as a potential treatment option for
97 resistant hypertension. This technique delivers low-level radiofrequency energy
98 throughout the renal artery wall to disrupt renal nerves and thereby modulate BP to some
99 extent. A number of observational studies and randomized controlled trials among non-
100 Chinese patients have demonstrated both the safety and the potential efficacy of this new
101 therapy⁷⁻¹⁵, whereas several other studies failed to show extra benefits when RDN was
102 applied¹⁶⁻¹⁸. Whenever doubts arise concerning the effectiveness of a therapeutic
103 approach, rigorously designed studies are warranted to furnish conclusive evidence.
104 According to the clinical consensus from the European Expert Group¹⁹, many factors
105 could affect the results of RDN in clinical trials, including procedural aspects, patient
106 populations, and design considerations. Many aspects of the RDN procedure may affect
107 the success of the ablation; furthermore, whether denervation has been completely
108 achieved in a specific patient remains the key factor for the efficacy of RDN.

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3 110 Together with these key recommendations¹⁹, we present the rationale and methodology
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5 111 for a randomized, controlled trial of RDN using a 5F saline micro-irrigated RFA for the
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7 112 treatment of hypertension in Chinese patients who have failed standardized
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9 113 pharmacologic therapy.
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13 14 115 **Methods/design**

15 16 17 116 **Study design**

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19 117 This trial ([ClinicalTrials.gov ID: NCT02900729](https://clinicaltrials.gov/ct2/show/study/NCT02900729)) is a multicenter, randomized, open-label,
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21 118 parallel-group, active controlled trial that will investigate the efficacy and safety of a 5F
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23 119 saline-irrigated RFA used in RDN for the treatment of Chinese patients with resistant
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25 120 hypertension. The RFA catheter under study is manufactured by Shanghai WiseGain
26
27 121 Medical Devices Co., Ltd. Approximately 13 clinical centers will participate in this trial.
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29 122 A brief flow chart of this trial is provided in [Figure 1](#).

30 31 123 **Study patients**

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33 124 A total of 254 patients who have failed pharmacological therapy will be enrolled. The
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35 125 following are the inclusion criteria:

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38 126 1. Subject with primary hypertension has 24-hour ambulatory SBP \geq 135 mmHg and
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40 127 office SBP \geq 140 mmHg /office diastolic blood pressure (DBP) \geq 90 mmHg after
41
42 128 4weeks'standardized triple therapy.
43
44 129 2. Subject is \geq 18 and $<$ 80 years old at the time of randomization.
45
46 130 3. Subject agrees to have all study procedures performed, and is willing to provide
47
48 131 written informed consent to participate in this clinical study.

49
50 132 The exclusion criteria are as follows:

- 51
52 133 1. Subject has acute or serious systemic infection.
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54 134 2. Subject has a history of renal artery interventional therapy.
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- 135 3. Subject lacks suitable renal artery anatomy for percutaneous renal sympathetic nerve
- 136 RFA surgery, including but not limited to the presence of serious aorta or renal-
- 137 artery tortuosity or renal-artery stenosis.
- 138 4. Subject has experienced a myocardial infarction, unstable angina pectoris, syncope,
- 139 or a cerebrovascular accident within three months of the screening period, or has
- 140 widespread atherosclerosis, with documented intravascular thrombosis.
- 141 5. Subject has aortic dissection aneurysm.
- 142 6. Subject has primary pulmonary hypertension.
- 143 7. Subject has an estimated glomerular filtration rate of less than 40 mL/min/1.73m²
- 144 according to the Modification of Diet in Renal Disease formula.
- 145 8. Subject had a definite diagnose of coronary heart disease requiring beta-blockers
- 146 9. Subject has Class III-IV heart failure or left ventricular ejection fraction <45%.
- 147 10. Subject has atrial fibrillation.
- 148 11. Subject has a significant bleeding tendency or blood system disease(s).
- 149 12. Subject has a malignancy or end-stage disease(s).
- 150 13. Subject has secondary hypertension.
- 151 14. Subject has type 1 diabetes mellitus.
- 152 15. Subject has other conditions inappropriate for participation, at the investigator's
- 153 discretion.
- 154 16. Subject has a medical ethics issue of concern, at the investigator's discretion, such as
- 155 presence of an average SBP \geq 170 mmHg on 24-hour ambulatory BP monitoring after
- 156 4weeks'standardized triple therapy.

157 **Recruitment process**

158 Before enrollment, there will be two screening visits. Each participant will be assigned a
159 unique identification number during the first screening visit. In addition to the above-
160 mentioned entry criteria, patients with primary hypertension who meet one of the three
161 following criteria will be considered for further evaluation at the second screening visit:

- 162 ● Adherence to 3 kinds of antihypertensive medication, office SBP \geq 140mmHg or
- 163 office DBP \geq 90mmHg, and office SBP <180mmHg, office DBP <100mmHg.

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- 164 ● Adherence to two kinds of antihypertensive medication, office SBP ≥ 140 mmHg, or
 - 165 office DBP ≥ 90 mmHg.
 - 166 ● Adherence to one kind of antihypertensive medication, office SBP ≥ 160 mmHg, or
 - 167 office DBP ≥ 100 mmHg.

11 For any initially eligible patients as mentioned above, three basic kinds of
12 antihypertensive medication, e.g. standardized triple antihypertensive medications
13 consisting of amlodipine 5mg per day, losartan potassium 50mg, and hydrochlorothiazide
14 12.5mg per day, will be administered for at least 4 weeks (run-in period). Patients who
15 meet the following BP threshold criteria will then be eligible for randomized assignment
16 after the second screening period: 24h ambulatory BP ≥ 135 mmHg and office SBP
17 ≥ 140 mmHg, or office DBP ≥ 90 mmHg.

175 **Randomization process**

176 Eligible patients with resistant hypertension will be randomly assigned to one of two
177 study treatment groups in a 1:1 ratio. A stratified block randomization with randomly
178 varying block size will be performed, stratified according to study site. Random
179 assignment is generated by an independent statistician and implemented via random
180 envelopes assigned to each site. These envelopes are opaque and without any information
181 identifying treatment assignment from appearance. Anyone is prohibited to open an
182 envelope unless there is a real eligible subject requiring randomization. In order to avoid
183 potential selection bias, the sequence is concealed from both clinical staff and patients
184 until assignment. Hence, neither investigators nor participants can influence which group
185 the study patients are assigned to.

186 **Description of the interventions**

187 The enrolled subjects will be randomized to undergo RDN using a 5F saline micro-
188 irrigated RFA plus antihypertensive medication, or to be treated with antihypertensive
189 medication alone. RDN will be performed according to the device's instructions for use.

190 The study patients will be advised to maintain baseline antihypertensive medication in the
191 first 90 days after randomization. However, the three baseline antihypertensive

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3 192 medications (e.g. calcium antagonist, angiotensin II receptor antagonist, diuretics) will be
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5 193 adjusted after randomization when clinically necessary. Criterion for dosage reduction:
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7 194 subjects experience a sudden reduction in BP within a short time, meanwhile
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9 195 accompanied by ischemic symptoms (weakness, dizziness, syncope, fall, etc.). If these
10
11 196 symptoms disappear and 72-hour average home SBP is ≥ 140 mmHg or DBP ≥ 90 mmHg,
12
13 197 the antihypertensive medication may be restored to the original type and dosage.
14
15 198 Criterion for dosage increase: if home SBP is ≥ 170 mmHg for an observational period of
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17 199 72 hours from randomization through 90 days, or from 91 days through 180 days if
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19 200 average home SBP is ≥ 140 mmHg or DBP is ≥ 90 mmHg based on three consecutive daily
20
21 201 measurements, the following three kinds of drugs could be added, one per month in
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23 202 sequence: aldactone 20mg per day, metoprolol succinate sustained-release tablet 47.5mg
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25 203 per day, and clonidine hydrochloride tablets 75ug t.i.d (Figure 1).

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27 204 For patients receiving antihypertensive medication alone, after maintenance of baseline
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29 205 standardized triple antihypertensive medications for 90 days post randomization and then
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31 206 medically necessary adjustment of antihypertensive medications for another 90 days,
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33 207 subjects will be allowed to cross over to undergo RDN if they still meet the original
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35 208 inclusion criteria for the study.

36 209 **Renal denervation procedure**

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38 210 Under local anesthesia, RDN procedures are to be performed by interventionists at each
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40 211 study site after a unified training session. Following preoperative preparation, the
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42 212 ablation catheter will be advanced to the distal segment of the renal artery through the 7F
43
44 213 guidance catheter.

45
46 214 The ablation involves at least six applications to each renal artery, according to the length
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48 215 of the artery's main stem. If the main renal artery is less than 15 mm, two ablations
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50 216 should be delivered to the main bifurcation with diameter > 3 mm in order to ensure six
51
52 217 ablation lesions on each side. Treatment begins from the distal end of the artery or the
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54 218 main bifurcation in a helical pattern as the catheter is pulled back.

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56 219 For every renal artery ostium, the catheter must be maneuvered to at least one position in
57
58 220 each of the distal, middle and proximal segments. The ablation energy will be 8-10W in
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221 the distal segment, 10-11W in the middle segment and 12W in the proximal segment. Each
222 ablation will last 60s. The ideal target outcome is for the energy titration to achieve a 10%
223 to 20% drop in impedance at each location. If the drop in impedance is less than 5%, or
224 the ablation energy is unable to achieve the preset wattage, the ablation will be stopped
225 and the catheter will be repositioned.

226 **Study visits**

227 Nine study visits will be scheduled following the baseline visit: once every 15 days in the
228 first 90 days and then every 30 days until 180 days. For the 3rd, 5th, 7th, and 10th visits
229 patients will return to the clinic office; for the remaining visits, the patients will be
230 consulted by phone. At every visit, data relating to BP, medication, adverse events, etc.,
231 will be collected. The 8-item Morisky Medication Adherence Scale (MMAS-8) will be
232 provided at 1st, 3rd, 5th, 7th, and 10th visits.

233 The subjects may withdraw from the study if any of the following conditions occur:

- 234 ● After 4 weeks post randomization, the office or home SBP is ≥ 180 mmHg for more
235 than one week while standardized antihypertensive medications are maintained.
- 236 ● Based on the investigator's discretion, the subject is no longer eligible for the study
237 for any reason.

239 **Outcome measures**

240 **Primary outcome**

241 The primary outcome of this study is the change in 24-hour average ambulatory SBP
242 from baseline to 3 months compared between the RDN-plus-medication group and the
243 medication-only group. The department of laboratory other than the clinical department
244 at each participating site will undertake the ambulatory blood pressure monitoring
245 (ABPM) during the study period. The ABPM machine will record and report ABPM
246 results automatically. This outcome will be strictly standardized in terms of uniform

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3 247 validated devices, appropriate cuff, identical clinical setting, and resting condition prior
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5 248 to BP measurement after mandatory one-day stay in participating site, etc.
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8 249 Secondary outcomes
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- 10 250 1. Change in office systolic/diastolic BP from baseline to 6 months post-
11 randomization.
12 251
13 252 2. Incidence of achieving target BP at 6 months post-randomization. Target BP is
14 defined as daytime ambulatory BP<135/85mmHg, nighttime ambulatory
15 253 BP<120/70mmHg, or average 24-hour ambulatory BP<130/80mmHg.
16 254
17 255 3. Incidence of substantially adjusting antihypertensive medications at 6 months
18 post-randomization. A substantial adjustment of antihypertensive medications is
19 256 defined as any change in the number or type of antihypertensive medications, or a
20 257 $\geq 50\%$ dose change in the last two weeks with respect to any ongoing
21 258 antihypertensive medications.
22 259
23 260 4. Incidence of achieving reductions of ≥ 5 mmHg, ≥ 10 mmHg, ≥ 15 mmHg, and ≥ 20
24 mmHg in BP, including ambulatory, office, and home BP at 6 months post-
25 261 randomization.
26 262
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28 263 Safety endpoints
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30 264 The safety endpoints mainly include any adverse events (e.g. puncture hematoma,
31 265 thrombosis, renal artery stenosis and renal artery dissection as adverse event of special
32 266 interest, etc), a change in renal function (serum creatinine, urea nitrogen, serum uric acid,
33 267 creatinine clearance, etc.), other laboratory tests (liver function, serum biochemistry), and
34 268 cardiovascular complications.
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46 269 **Sample size calculation**
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49 270 We used R V.3.2.3 (R Core Team. R: A language and environment for statistical
50 271 computing. Vienna, Austria: R Foundation for Statistical Computing,
51 272 2014.<http://www.R-project.org/>; last accessed June 2016) to estimate sample size. The
52 273 trial is designed to compare the difference in average ambulatory SBP as a change from
53 274 baseline to 3 months between the RDN-plus-medication group and the medication-alone
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4 275 group. With a sample size of 108 randomized patients per group, the between-group
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6 276 comparison will be powered at 90% to establish the superiority of added RDN for the
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8 277 primary endpoint at a two-sided significance level of 0.05, assuming that the true SBP
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10 278 difference is 8 mmHg with a common standard deviation of 18 mmHg. Given an
11
12 279 expected dropout rate of 15% in the first 3 months post randomization, a total of 254
13
14 280 patients (127 patients per group) must be enrolled in the study.

15 281 Results of 10,000 simulations using this estimated sample size for each study showed that
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17 282 an empirical power of 98% would be reached for the analysis of the BP target rate (56%
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19 283 versus 44%) as the important efficacy endpoint, using the Cochran-Mantel-Haenszel
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21 284 (CMH) test with antihypertensive medication adjusted or not within the last 2 weeks as
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23 285 stratification factor.

24 286 **Statistical analysis**

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27 287 The full analysis set, according to the intent-to-treat principle, will be established as the
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29 288 primary analysis population. A two-sided p-value of <0.05 will be considered to indicate
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31 289 significance for any statistical tests. R, V.3.2.3 and SAS software, V.9.2 (SAS Institute,
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33 290 North Carolina, USA) will be used for statistical analysis. Such data as demographics,
34
35 291 baseline characteristics, and safety will be summarized according to treatment group.

36
37 292 The primary efficacy outcomes will be analyzed using analysis of covariance (ANCOVA)
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39 293 with treatment group as fixed factor and BP values at baseline as covariate. The sensitivity
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41 294 analysis with stratifying variable centre as a fixed effect of ANCOVA will also be considered as
42
43 295 appropriate. The paired and unpaired t-tests will further be used to test BP reduction
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45 296 within each group and between groups, respectively. The 95% confidence intervals for
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47 297 the differences between treatment groups will also be calculated. Subgroup analyses are
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49 298 prespecified according to the following prognostic factors: sex, age, diabetes, body mass
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51 299 index, estimated glomerular filtration rate, and aldosterone use at baseline.

52 300 Blood pressure target rate at 6 months will be analyzed using the CMH test, with
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54 301 antihypertensive medication adjusted or not within the last 2 weeks as stratification factor.

55 302 Other categorical data will be tested using Pearson's chi-square test or Fisher's exact test,
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57 303 as appropriate. Other continuous efficacy endpoints will be analyzed similarly to the
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3 304 primary endpoint. Mixed-model repeated measures analysis including terms for treatment
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5 305 group, time, baseline measurement, and time by treatment group interaction will be
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7 306 considered to compare BP reduction in the study.
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11 308 **Discussion**

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15 309 The design and methods of this trial satisfy the requirements to test whether a 5F saline
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17 310 micro-irrigated RFA used in RDN is safe and effective for patients who remain
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19 311 hypertensive despite adherence to polypharmacy.

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21 312 With the recognition of the role of the sympathetic nervous system in the development
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23 313 and progression of hypertension^{20, 21}, catheter-based RDN has been developed to reduce
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25 314 sympathetic nervous activity and subsequently reduce BP, as well as mortality and
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27 315 morbidity, in patients with uncontrolled hypertension²²⁻²⁵ and the prevention of
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29 316 recurrences of atrial fibrillation²⁶, the improvement of glycemic control²⁷ and the
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31 317 mitigation of pulmonary arterial hypertension as well²⁸. However, the clinical evidence in
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33 318 support of RDN as an effective interventional technique in patients with resistant
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35 319 hypertension appears conflicting. Several large studies support both the safety and the
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37 320 efficacy of this new therapy⁷⁻¹⁵, but some studies failed to show the superiority resulting
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39 321 from added RDN¹⁶⁻¹⁸. In view of this controversy, the European Expert Group convened
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41 322 a clinical consensus conference and agreed on recommendations for future randomized
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43 323 controlled trials of RDN in hypertension. The design and methods of our trial accord in
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45 324 principle with the recommendations.

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47 325 The RDN procedure is so complex that the efficacy of ablation may be influenced by
48
49 326 many factors, such as renal artery anatomy, the depth of the ablation lesion,
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51 327 atherosclerosis, etc. Achieving complete ablation will pose a challenge to the operator,
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53 328 the equipment, and the procedure. A study of the anatomic assessment of sympathetic
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55 329 peri-arterial renal nerves showed that the greatest number of nerves were observed in the
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57 330 proximal and middle segments of the renal artery, while the smallest number were seen in
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59 331 the distal segment. However, in the main renal artery, the distance from the nerve to the
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332 renal artery lumen is shorter than in the proximal and middle segments, being

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3 333 approximately 4.28mm²⁹. Another study showed that, for a patient with atherosclerosis,
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5 334 the RFA-induced damage did not penetrate deeper than 2mm from the luminal surface,
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7 335 leaving unaffected a large part of the nerves in (peri-) adventitial areas remote from the
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9 336 vascular lumen³⁰. An animal study showed that the ablation zone geometries varied in arc,
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11 337 area, and depth, depending on the composition of the adjacent tissue substructure³¹. In
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13 338 addition, the delivered power density was influenced by tissue substructure, and peaked
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15 339 at the conductivity discontinuities between soft fatty adventitia and water-rich tissues, not
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17 340 at the electrode-tissue interface³¹. With a greater recognition of nerve distribution, the
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19 341 ablation depth and location should be taken carefully into account.

20
21 342 In previous studies, a non-irrigated catheter was usually used and the ablation energy was
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23 343 usually 8W. Increasing ablation energy or prolonging ablation time could make the
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25 344 ablation deeper. However, using a non-irrigated catheter could raise the temperature of
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27 345 the luminal surface too much to increase the ablation power. In this study, radiofrequency
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29 346 energy delivery with the use of cold saline irrigation seems safe and effective. By
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31 347 actively cooling the ablation electrode during RFA, it is possible to minimize the
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33 348 possibility of char formation and also decrease the probability of vasospasm. These
34
35 349 advantages to saline irrigation are so significant that most cardiac ablations are now
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37 350 performed using irrigated ablation catheters³². Ahmed et al., in a small single-arm study,
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39 351 demonstrated that RND can be performed safely and effectively using a saline-irrigated
40
41 352 RFA in patients with hypertension³³. Using a saline-irrigated catheter, with the protection
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43 353 of cold saline, higher ablation energy can be delivered, ensuring the ablation depth.
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45 354 Indeed, the saline-irrigated catheter has been widely used in cardiac ablation.

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47 355 In most clinical trials involving RDN, adrenal artery less than 4mm in diameter could not
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49 356 be ablated because of the limited operation equipment. In this study, the 5F saline micro-
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51 357 irrigated RFA catheter is smaller and more flexible, so it can be used in renal arteries
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53 358 with diameter <4mm, while minimizing the possibility of peripheral artery-related
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55 359 complications.

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57 360 In this study, the operation procedure will also be unified. A similar spiral ablation will
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59 361 be used and at least one site must be ablated at each of the distal segments of the renal
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362 artery, the middle segment, proximal, and opening. Four quadrants will be ablated. There

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3 363 are a total of 6 ablation points on each side of the renal artery. The ablation energy will
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5 364 also be standardized to ensure sufficient ablation.
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8 365 In this trial, patients with 24-hour ambulatory SBP ≥ 135 mmHg and office SBP
9 366 < 170 mmHg will be eligible for enrollment, while patients with high-risk characteristics
10 367 will be excluded. Given this restriction, the patients enrolled in this study will mostly
11 368 have mild to moderate hypertension and might be more responsive to RDN-induced
12 369 changes in sympathetic tone. In addition, it will be safer for these patients to strictly
13 370 follow a standardized medication regimen. Moreover, higher drug adherence will be
14 371 expected in this study, because of the lower level of discomfort occurring in the
15 372 management of mild to moderate rather than severe hypertension.
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23 373 In the study period, the antihypertensive medications administered are explicitly specified:
24 374 standardized triple antihypertensive medications include a calcium channel blocker, a
25 375 renin-angiotensin system blocker, and a diuretic. In the Symplicity HTN-3 study¹⁶, the
26 376 maximum doses were administered, and 39% patients required medication adjustment
27 377 because of adverse events; this may be related to the negative conclusions of that study.
28 378 Conversely, in the DENERHTN study¹⁵, the antihypertensive medications in the RDN
29 379 group and control group were strictly regulated, and the study results supported the
30 380 superiority of RDN. The rigorous specification of medication may be an important factor
31 381 influencing the study results.
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39 382 For this study, ambulatory BP is used as the primary endpoint, and office BP as the
40 383 secondary parameter. In fact, several previous studies have documented a better
41 384 prognostic value of ambulatory over office BP in different populations³⁴⁻³⁸. Among the
42 385 previous trials conducted on RDN, only the DENERHTN study¹⁵ successfully used the
43 386 change in mean daytime ambulatory SBP as primary endpoint, and that study found RDN
44 387 to have superior efficacy. The Expert Group also strongly recommended ambulatory BP
45 388 as the primary measure of response to RDN. Using ambulatory BP monitoring to measure
46 389 efficacy could exclude pseudo-resistance due to a “white-coat” effect.
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55 390 There is also one limitation regarding the selection of the control group. Because of the
56 391 poor acceptability by patients in our routine clinical practice and potential ethical
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4 392 problems, a sham operation will not be performed in this study; its omission might thus
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6 393 be a potential confounder for study outcomes. Although a sham procedure could reduce
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8 394 some Hawthorne effects, it could not eliminate other biases that are considered as reasons
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10 395 for the lack of benefit from RDN.

11 396 **Ethics and dissemination**

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14 397 This trial will be conducted in accordance with the principles outlined in the Declaration
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16 398 of Helsinki and will follow the Consolidated Standards of Reporting Trials (CONSORT)
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18 399 statement (<http://www.consort-statement.org/>). It has been approved by the Independent
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20 400 Ethics Committee for each site (Approval No 2016-46). All subjects will be required to
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22 401 sign a written informed consent document before their participation in the trial.

23
24 402 This study is designed to investigate the efficacy and safety of RDN using a 5F saline-
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26 403 irrigated RFA in Chinese patients with hypertension who are resistant to medication
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28 404 therapy. Its goal is to provide clinical evidence that RDN with a 5F saline-irrigated RFA
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30 405 is both safe and effective in Chinese patients with drug-resistant, systemic hypertension.
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32 406 Findings will be shared with participating hospitals, policymakers and the academic
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34 407 community to promote the clinical management of resistant hypertension in China.

35 36 37 38 409 **Trial status**

39
40 410 The study enrolled the first patient in March 2017 and is expected to finish patient
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42 411 enrolment within 1.5 years.

43 44 45 412 **Competing interests**

46
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52
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56 57 417 **Contributors**

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2
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4
5 419 power analyses and wrote the data analysis section. ZJL and JBG bear overall
6
7 420 responsibility for the design, ethical conduct and publication of the study. Administrative,
8
9 421 technical and material support was provided by ZJL and LS. All authors involved the
10
11 422 protocol discussion and they will take responsibility for study data gathering and
12
13 423 verification. All authors edited the draft and contributed substantially to the manuscript;
14
15 424 they all approved this submission.

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3 543 [Figure 1](#): Study flowchart and principles of adjusting antihypertensive medications
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6 544 Abbreviations: ABPM: Ambulatory Blood Pressure Monitoring; BP: Blood Pressure;
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8 545 DBP: Diastolic Blood Pressure; RDN: Renal Denervation; SBP: Systolic Blood Pressure
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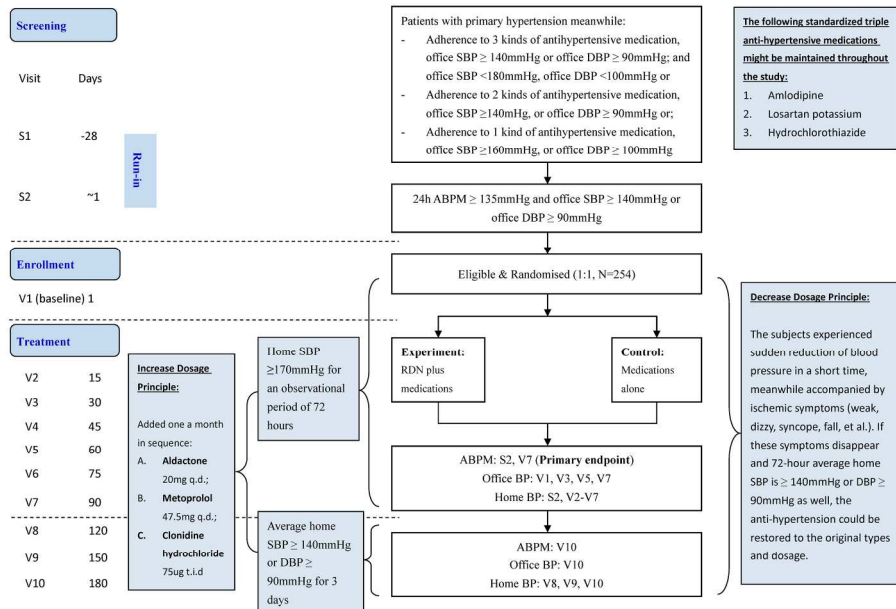


Figure 1: Study flowchart and principles of adjusting antihypertensive medications
 Abbreviations: ABPM: Ambulatory Blood Pressure Monitoring; BP: Blood Pressure; DBP: Diastolic Blood Pressure; RDN: Renal Denervation; SBP: Systolic Blood Pressure

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SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p.3
	2b	All items from the World Health Organization Trial Registration Data Set	n.a.
Protocol version	3	Date and version identifier	n.a.
Funding	4	Sources and types of financial, material, and other support	p.16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p.1, 2, 16
	5b	Name and contact information for the trial sponsor	p.1, 2, 16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	p.21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	p.21
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p.5, 6
	6b	Explanation for choice of comparators	p.5, 6

Section/item	ItemNo	Description	Addressed on page number
Objectives	7	Specific objectives or hypotheses	p.6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p.6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p.6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p.6, 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p.8,9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p. 9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	p.8, 9, 10, figure 1
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	p.8, 9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p.10, 11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants.	figure 1

Section/item	ItemNo	Description	Addressed on page number
		A schematic diagram is highly recommended (see fig 1[f1])	
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p.11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n. a.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers) and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p.8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p.8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p.8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts) and how	p.8
	17b	If blinded, circumstances under which unblinding is permissible and procedure for revealing a participant's allocated intervention during the trial	p.8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires,	Figure 1

Section/item	ItemNo	Description	Addressed on page number
		laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p.18-19
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	n.a.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p.12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p.12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p.12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n.a.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n.a.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p.15

Section/item	ItemNo	Description	Addressed on page number
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n.a.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p.6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n.a.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p.20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p.20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p.16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	p.20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	p.18
Dissemination	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and	p.20

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Section/item	ItemNo	Description	Addressed on page number
policy		other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
	31b	Authorship eligibility guidelines and any intended use of professional writers	p.16
	31c	Plans, if any, for granting public access to the full protocol, participant level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n.a.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.