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EUnetHTA JA2 WP7 DELIVERABLE

Core protocol Pilot for Additional Evidence Generation



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Core protocol Pilot for Additional Evidence Generation

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Institute for Quality and Efficiency in Health Care

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Table of Contents

INTRODUCTION	5
PROJECT FLOWCHART	8
SECTION 1. TEMPLATE OF A CORE PROTOCOL FOR AEG	9
1.1 REQUEST TO WP7 SG2 PARTNERS FOR PROTOCOL TEMPLATES.....	10
1.2 GLOSSARY OF TERMS.....	12
1.3 PROPOSAL OF “CORE ELEMENTS”	14
1.3.1. ALL ELEMENTS OF A STUDY PROTOCOL.....	14
1.3.2. “CORE ELEMENTS” - TEMPLATE OF A CORE PROTOCOL FOR AEG.....	16
1.3.3. “ADDITIONAL ELEMENTS”	21
1.4 BIBLIOGRAPHY OF THE FIRST SECTION.....	24
SECTION 2. PILOT ON RENAL DENERVATION – CORE PROTOCOL FOR AEG FOR RENAL DENERVATION	25
APPENDIX 1 - TOPIC SELECTION PROCESS	44
APPENDIX 2 - UPDATE OF THE EXISTING HTA REPORT ON THE SELECTED TOPIC	45

INTRODUCTION

Within EUnetHTA Joint action 2, Subgroup 2 of Work package 7 (WP7 SG2) is dedicated to Additional Evidence Generation (AEG) with the objective of developing and testing a methodological basis for European cooperation in this field. The ‘Core protocol Pilot for AEG’ is one of the deliverables of WP7 SG2 and has to be read in association with two methodological documents:

- **Position paper on how to best formulate research recommendations (developed by ASSR and avalia-t)**
- **Position paper on how to decide on the appropriate study design (developed by NETSCC).**

Background

The uncertainty relating to a lack of, or inadequate evidence, at the time of appraisal is often an obstacle to the introduction of new technologies, or their permanence, into a health system. In these situations, the decision makers may either delay the introduction of a new technology and wait for stronger evidence, with the risk of delaying potential benefits to patients; or may approve technologies that may later turn out to have a low benefit-risk ratio or even prove to be harmful.

Several countries have therefore developed mechanisms that allow temporary access to promising technologies, requesting at the same time the generation of additional evidence to reduce uncertainty.

A five-step pathway for AEG mechanisms may be outlined:

1. a first HTA with identification of knowledge gaps\ evidence gaps;
2. a decision conditional to evidence generation;
3. generation of the additional evidence requested;
4. a HT re-assessment integrating the new evidence;
5. a revised decision on the basis of the new available evidence, which may lead to continue the use (widespread or restricted) or discontinue it. (Figure 1)

The Generation of the Additional Evidence may include trials, observational studies, registries, data on appropriateness of use etc. and aims at reducing the detected uncertainty.

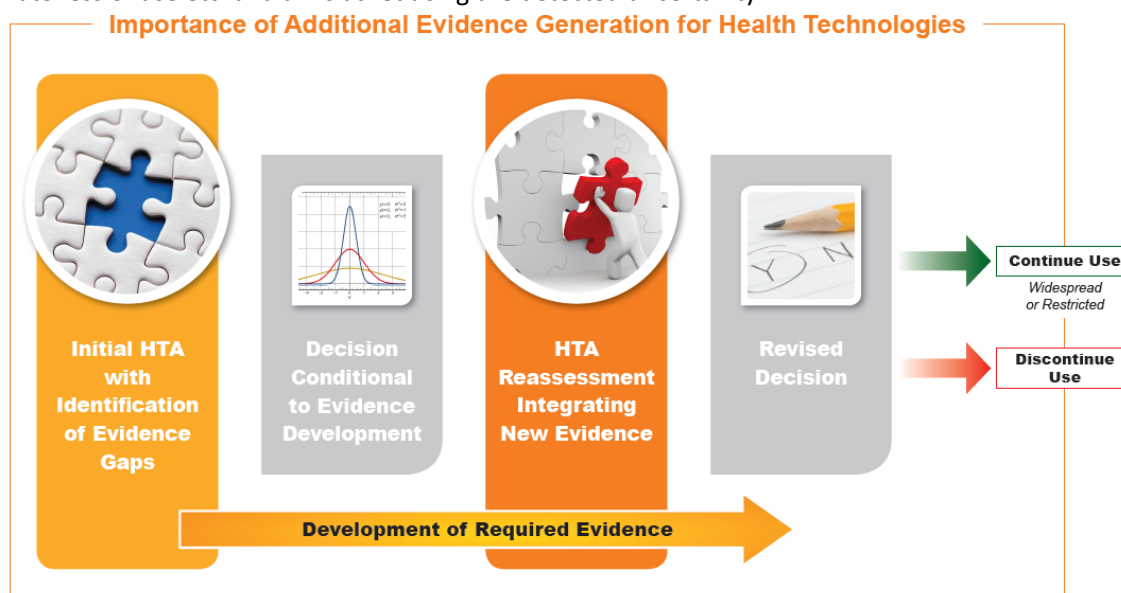


Figure 1. Pathway of additional evidence generation for health technologies¹

The idea behind this pilot was to endorse collaboration on AEG. European collaboration on AEG can be realized

¹ “Improving Additional Evidence Generation for health technologies”. Poster developed by The French National Authority for Health (HAS) for EUnetHTA conference 2014.

through either common requests (e.g. several countries wishing to set up a multicentric study) or coordinated requests (e.g. several countries asking for national studies, but in a coordinated manner, in order to obtain comparable data).

Against this background, this pilot aimed to suggest which items of a study protocol are key for collaboration (necessary to determine whether the study would fill-in the evidence gaps or not) and that are at the same time “shareable” among partners. These items were called “core” elements².

Consequently, the idea was to propose a template containing these core elements, **the Core protocol template for Additional Evidence Generation**, that could be used as a basis when requesting an AEG and which could be utilized by different countries. Countries should be aligned and agree on these core elements when requesting an AEG if they want to collaborate.

In practice, the Core protocol template for AEG is directed to both HTA agencies\national bodies and to study sponsors. HTA agencies can use it as a basis to set up requirements for a common study or multiple coordinated AEG requests. For sponsors it can serve as guidance when drafting their study protocols. Additional elements should be developed by those who are going to set up the study in practice.

This template is meant to be used for AEG studies and thus should be drafted\filled-in after the identification of an evidence gap and before or after the decision on coverage with evidence generation, depending on the coverage with evidence generation system that is in place.

Objectives

This pilot consists of two parts:

- **Developing a template of a core protocol for Additional Evidence Generation (section 1).**
The objective of this part is to define the “core elements” of a study protocol for Additional Evidence Generation, and develop a template, based on these core elements, that could be used in different countries (Core protocol template for AEG).
Having this template defined and used should allow, when needed, the collection of consistent and poolable data in order to cover a specific evidence gap.
- **Testing the developed template and SG2 methodological papers on a practical example (section 2).**
The objective of this part is to test the developed template, but also two other WP7 SG2 methodological papers³, on an example technology in need of AEG identified in an HTA report. This exercise should assess the feasibility of coordinating an AEG request in Europe.
The output is a document containing advice on evidence gaps and all specified core elements that are necessary to produce the additional evidence needed on the example technology.
The information is presented in the form of a study protocol, but which contains only “core elements”.
In order to be implemented and further used, the Core protocol needs to be completed with further information (“additional elements”), and adapted to specific national requirements, if needed.

The final deliverable is the Core protocol document and not a study conduct. Study funding and implementation are not within the scope of EUnetHTA.

² For example the definition of the population of the study or the choice of the outcome were considered core elements because they are related to methodological appropriateness, and should be shared when collaborating on a specific AEG request in order to collect the same information\evidence. On the contrary, all other elements that deal with setting up the study in practice, for example the data management and administrative information, were considered as “additional elements” (see section 1 for a detailed explanation).

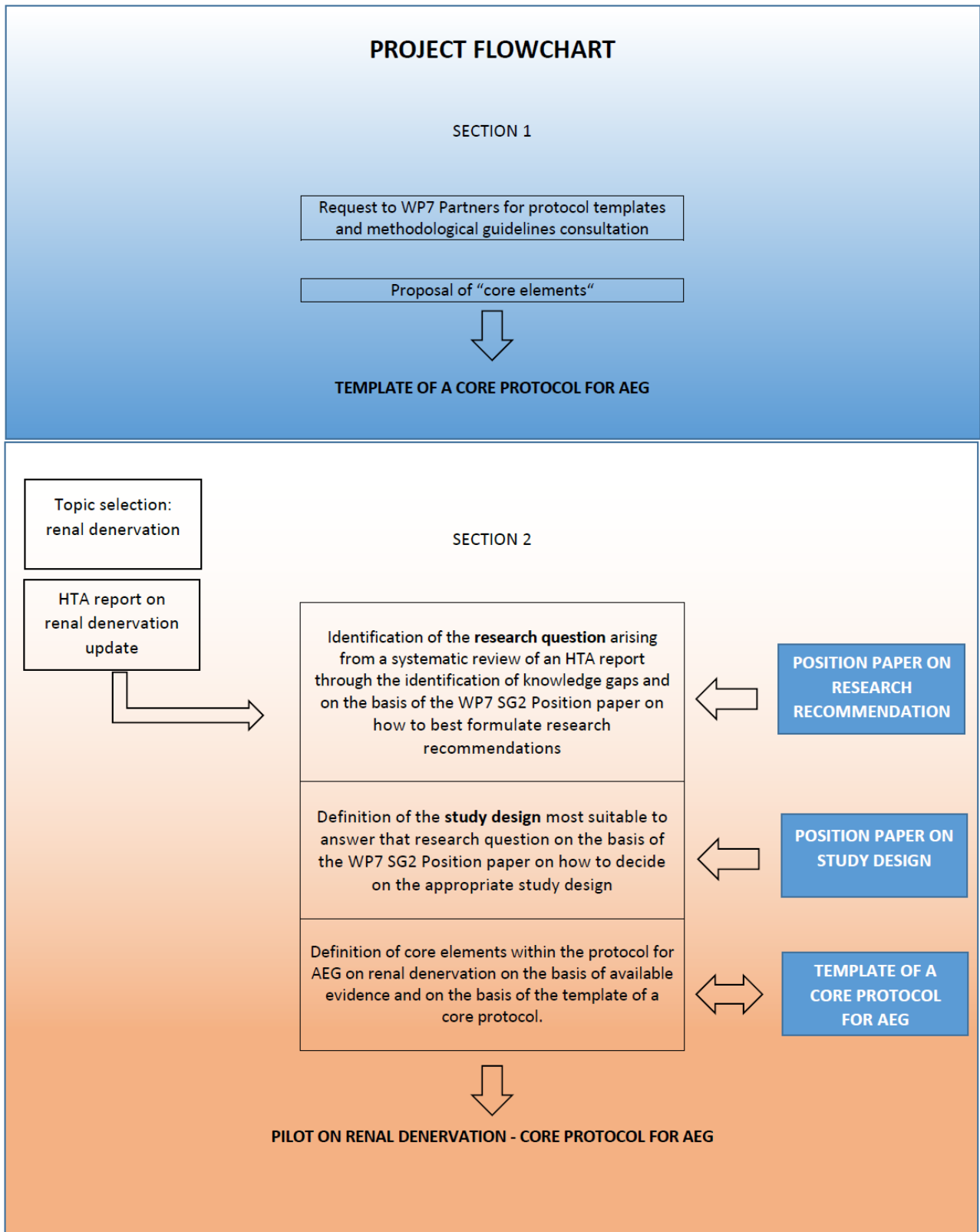
³ WP7 SG2 Position paper on how to best formulate research recommendations and WP7 SG2 Position paper on how to decide on the appropriate study design.

The project's steps and methods

- Topic selection process: selection of the technology for the second part of the pilot (February-July 2014)⁴
- Project scoping (July-September 2014)
- Development of the first draft (October 2014-February 2015 (topic changed in November 2014))
- WP7 review of the first draft (March 2015)
- SAG, manufacturers', EMA and ENCePP review of the upgraded version of the first draft (May-June 2015)
- Development of the second draft (June-July 2015)
- Public consultation (July-August 2015)
- Finalization and publication (September 2015).

Methods used to produce this document are presented in the flowchart on the next page. More details related to the development of the sections 1 and 2 are presented at the beginning of each section.

⁴ For more details please refer to Appendix 1.



SECTION 1. TEMPLATE OF A CORE PROTOCOL FOR AEG

The aim of this section is to define “core elements” of a study protocol for Additional Evidence Generation (AEG) and develop a template called “Core protocol template for AEG”, containing these core elements, which could be used in different countries and help to collect consistent and poolable data needed to fill a specific evidence gap.

There are many methodological guidelines which can be followed in order to write a study protocol, which may have different features in relation to the type of study considered. In this section we present a proposal of the core elements, which should be addressed in a study protocol for Additional Evidence Generation (AEG). These elements have been defined according to the retrieved methodological guidelines (3-10), the templates provided by EUnetHTA partners (only three received at the moment of the document drafting) and suggestions coming from EUnetHTA partners. Examples of study protocols were also consulted.

For the sake of this pilot, the elements of a study protocol have been classified in two levels:

- “core elements”, which are related to methodological appropriateness and necessary to ensure that the study will fill-in the gaps;
- “additional elements”, which are strictly related to the implementation of the study.

Protocol items that were considered key for collaboration and shareable were classified as “core elements”. These elements are essential methodological elements, which cover the theoretical aspects that are necessary to produce the additional evidence needed in order to fill the evidence gap of a technology and support the rationale of the study.

The “core elements” are supposed to be common and not specific for a particular type of study (interventional, observational etc.) or for the technology involved (drug, medical device etc.). Core elements should be of a general nature and thus transferrable into different settings/applicable in different countries.

The Core protocol template for AEG contains only core elements of a protocol.

Of course, a complete study protocol should include many other items in addition to core elements, which were called “additional elements” in this pilot. Having both “core” and “additional” elements is mandatory to evaluate the real study implementation/feasibility, but core elements alone should be sufficient to ensure the study to be designed in the right way to fill the evidence gap identified in a HTA report.

“Additional elements” are, on the other hand, proper to study implementation and more specific for setting up the study in practice. They could be considered in the national context after the definition of common core elements.

Consequently, the core elements of this template should be integrated with additional elements in a complete study protocol, according to specific national requirements.

In order to be clear, a list of all elements that should be present in a study protocol will be presented first in a ranked order; then a clear distinction between “core” and “additional” will be performed in the following pages.

The core elements, forming the Core protocol Template for AEG, are fully described in this document, while additional elements (with some details) are only listed for information purposes.

Only the elements defined here as core elements are developed in the section 2 of the document.

1.1 REQUEST TO WP7 SG2 PARTNERS FOR PROTOCOL TEMPLATES

In order to collect any template currently used, we performed a query among EUnetHTA WP7 SG2 partners, and asked them if their agency has:

- a template of a protocol for Additional Evidence Generation (e.g. in the framework of post-introduction or coverage with evidence development schemes)
- or any other document/protocol template that might be of help for defining core elements of a protocol for Additional Evidence Generation.

Answers received:

AGENCY	TEMPLATE OF A PROTOCOL FOR AEG OR OTHER
HAS (France)	yes ⁵
ZIN (Netherlands)	yes ⁶
SNHTA (Switzerland)	no
SBU (Sweden)	no
IQWiG (Germany)	no
TLV (Sweden)	no
AETSA (Spain)	no
NETSCC (U.K.)	Answer missing
Agenas (Italy)	no
DHMA (Denmark)	Answer missing
GYEMSZI (Hungary)	no
VASPVT (Lithuania)	no
Osteba (Spain)	Answer missing
ASSR (Italy)	no
AVALIA-t (Spain)	no ⁷
NOKC (Norway)	no
NCPRMP (Bulgaria)	Answer missing
INFARMED (Portugal)	Answer missing
ISC III (Spain)	no
HIS (U.K.)	no
NICE (U.K.)	yes ⁸
HVB (Austria)	no
Ministry of Health Czech republic	Answer missing
AIFA (Italy)	no

⁵ Guide on post-authorization studies, HAS. «Les études post-inscription pour les technologies de santé (médicaments, dispositifs médicaux et actes), Modèle de protocole»(12)

⁶ Research proposal of the core study, ZIN “Voorwaardelijke toelating tot het basispakket geneeskundige zorg Basisdocument”(11)

⁷ Do not have an AEG protocol per se, but the document “Post-introduction Observation of Health Technologies. A methodological guideline” provides guidance on the development of a study protocol. (14)

⁸ UK Integrated Research Application System (IRAS), which is a web-based system for preparing applications used to obtain ethical and regulatory sign-off. This is not a template for AEG, but a set of details of the research project (core study information and additional information) requested to obtain the approval from different review bodies. (13)

Only 2 agencies answered that they have a protocol for AEG, one shared a national form to obtain approval for research, and 15 agencies answered they don't have it. It should be noted that, according to WP7 SG2 survey performed in 2013, some of the agencies that did not answer the aforementioned request have a limited experience with Additional Evidence Generation, or no experience at all.

1.2 GLOSSARY OF TERMS

TERM	DEFINITION
AEG	Additional Evidence Generation
Blinding	A procedure to ensure that one or more parties to the study are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to 2 parties (typically the subject(s) and the investigator(s) being unaware of the treatment assignment(s). However, there is no consensus about which two people are being blinded and hence this should be specified in any protocol.
Clinical outcome	It describes a valid measure of clinical benefit due to treatment: the impact of treatment on how a patient feels, functions and survives. Clinical outcome may be a clinical event (e.g. mortality, morbidity and/or health-related quality of life).
Comparator	A product\therapy used as a reference in a clinical study, which may be an active control, placebo or no treatment.
Confidentiality	The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.
Effectiveness	A measure of whether an intervention works, and how well it works, under the usual circumstances of health care practice (real clinical setting). Effectiveness studies tend to collect more comprehensive endpoint measures that reflect the range of benefits expected from the treatment that are relevant to the patient and to the payer (weaker link to mechanism of action).
Efficacy	A measure of whether an intervention works, and how well it works, under ideal circumstances. Efficacy studies tend to favour condition-specific endpoints with strong links to mechanism of action.
Good clinical practice (GCP)	International ethic and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.
GRADE	Grading of Recommendations Assessment, Development and Evaluation, a tool for grading the quality of healthcare. http://www.gradeworkinggroup.org/
Informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Investigator	A person responsible for the conduct of the research at a specific study site.
PICO	Acronym for Population, Intervention, Comparison, Outcome
Pragmatic RCTs	RCTs which are based in the real practice. They are set up in a group of people that resembles more the general population with the condition to be treated and they normally involve a treatment or intervention that is already in use in clinical practice. If an active comparator is chosen, it allows direct comparison against current practice's treatments to determine which is superior. The treatment (or intervention) received by the patient is randomly allocated in the normal way for RCTs.
Randomization	The process of assigning study subjects to treatment or control groups using an

	element of chance\ a random process.
RCT	Randomized controlled trial
RDN	Renal denervation
Sponsor	An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical study.
Study population	The subjects included in the study
Surrogate outcome	Outcome that is intended to replace a clinical outcome of interest that cannot be observed in a trial; it is a variable that provides an indirect measurement of effect in situations where direct measurement of clinical effect is not feasible in a reasonable timeframe or practical.
WP7 SG2	Work Package 7 of EUnetHTA Joint Action 2, Subgroup 2

1.3 PROPOSAL OF “CORE ELEMENTS”

The list of all elements that should be present in a study protocol is presented first (1.3.1); followed by the proposal of the Core Protocol Template for AEG (1.3.2; Figure 2) and the additional elements listed for information purposes (1.3.3).

The list of all elements as presented in sections 1.3.1. to 1.3.3. is intended to cover both interventional and non-interventional study designs and different study objectives. It is not necessarily a standard format for the protocol presentation, rather a set of elements which should be addressed in a study protocol for AEG. According to study type and objectives, the use of a specific protocol presentation format may be required by regulation and regulatory guidance (e.g. when study qualifies as a PASS - post-authorisation safety studies).

1.3.1. ALL ELEMENTS OF A STUDY PROTOCOL

- **Title**
- **General and administrative information**
- **Synopsis**
- **Study background**
- **Rationale of the study**
- **Research question**
- **Research methods:**
 - Study Design
 - Study population
 - Intervention and comparator
 - Study outcomes
- **Study procedures and procedures to avoid bias**
- **Data management**
- **Statistical aspects**
 - Sample size calculation
 - Statistical analysis
- **Setting, duration and follow up**
- **Adverse events and safety monitoring**
- **Administration of the study**
- **Quality Control and Quality Assurance**

- **Direct Access to Data and Monitoring**
- **Ethics and protection of human subjects**
- **Data Handling and Record Keeping**
- **Publication Policy**
- **Financing and insurance**
- **Project management**
- **Bibliography**

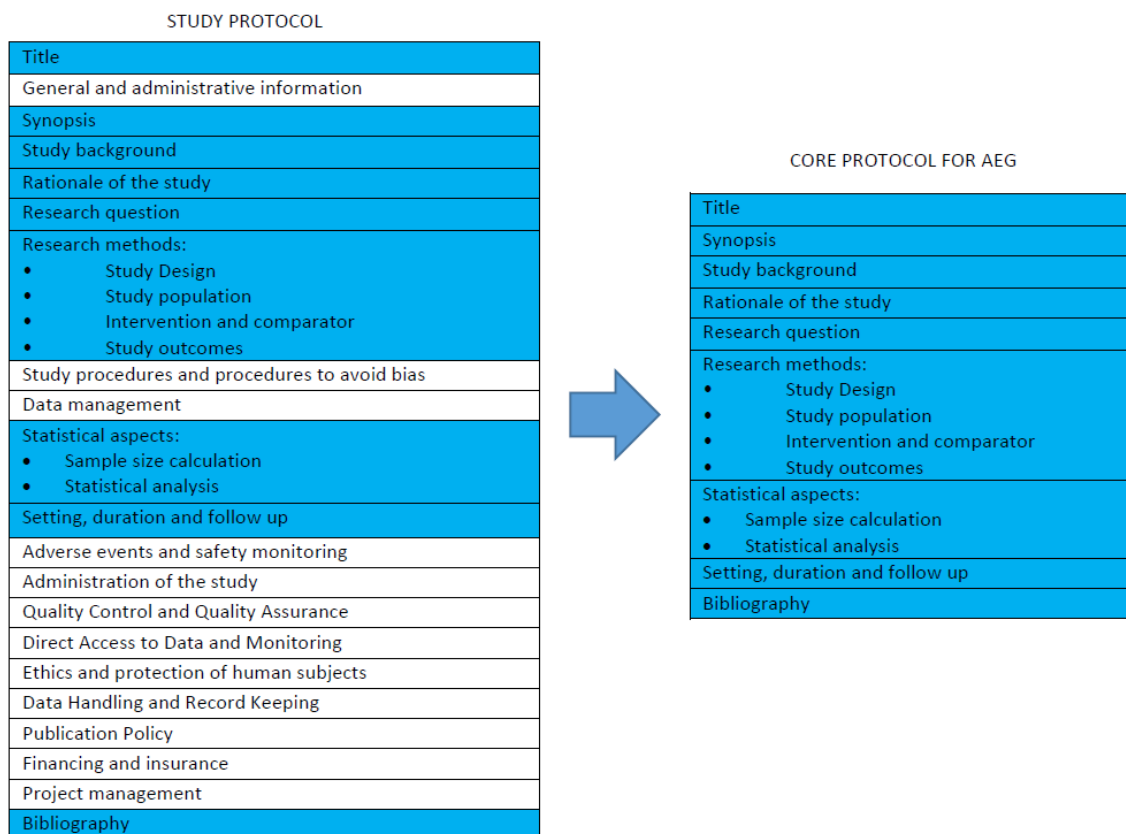


Figure 2. Elements of a study protocol and proposal of the Core Protocol Template for AEG

1.3.2. “CORE ELEMENTS” - TEMPLATE OF A CORE PROTOCOL FOR AEG

TITLE

Title of the Additional Evidence Generation Topic.

SYNOPSIS

Schematic abstract of the study which collects the key information of the protocol and allows to understand the basis of the study design. It can be included in a table and subdivided in sub-sections (such as title, rationale, background, study design, population etc.).

STUDY BACKGROUND

This section should provide the necessary background to understand the rationale and relevance of the study. It should support the purpose of the research and describe the context of the study.

For this reason, this section should include:

- description of the population and the disease \burden of the disease;
- name and description of the investigation\investigational product;
- role of health technology in the clinical scenario\strategy and its contribution to the current management of the disease, available alternatives and recommendations of latest clinical guidelines;
- all information on the technology needed\required in order to demonstrate the rationale for its intended clinical use and its safety and effectiveness profile. This is important because it means stating, before looking at the available evidence on the technology of interest, what is necessary to know in order to assess the technology;*
- summary of the available literature (evidence) on the health technology. Literature on clinical efficacy, effectiveness and safety should be derived from a relevant systematic review, HTA-report or a systematic search with predefined and relevant inclusion criteria; and updated if needed. This summary may contain published or unpublished data, animal and human studies, clinical studies and previous epidemiologic studies. It should cite the findings of similar studies. References may be cited in the background section. It is also useful to explain emerging evidence gaps.
The available evidence could be matched\compared with the information required to demonstrate the rationale of the technology. This exercise helps to identify evidence gaps*;
- description of on-going studies (which may be identified from searches in the ICTRP database, www.clinicaltrials.gov).

* These two points can be developed and obtained in practice following the WP7 SG2 Position paper on how to formulate research recommendations (for primary research arising from HTA reports). According to this position paper, these two concepts are called, respectively: *building the evidence profile of a technology* and *transferring the assessment results of the HTA report into the technology's evidence profile, to highlight evidence gaps*.

RATIONALE OF THE STUDY

The rationale specifies the reasons for conducting the research in light of the current knowledge. It should report an evidence based argumentation for the need of Additional Evidence Generation:

- the reasons for which the study should be conducted, in particular which gaps in knowledge the study is intended to fill;
- the relevance of the study (what the study adds or how it is different from other research studies that

- have already been done and a discussion about why the proposed study is preferable⁹ to on-going studies, since there might be on-going studies that should be awaited);
- the expected outcomes of the study (how the study will contribute to advancement of knowledge, how the results will be used, not only in publications but also how they will likely affect health care, health systems, or health policies).

RESEARCH QUESTION

In this section the research question of the study should be described. It should be clearly stated and it should be consistent with the study rationale explained in the previous section.

It should be formulated according to the PICO format and followed by an explanation on why the uncertainty is considered critical¹⁰.

Any pre-specified hypothesis should be included.

RESEARCH METHODS

Study design

The overall study plan and design should be described briefly but clearly in this section¹¹. A justification of the design chosen should be specified and the strength of the study design to answer the research question explained.

The type of study to be conducted should be specified: interventional (experimental) clinical trial, observational study, modelling study, etc.

For interventional studies, it should be specified whether it is a controlled study or not, the kind of control (e.g., placebo, no treatment, active treatment, historical), method of assignment to treatment (e.g. randomization or not), method of blinding (e.g., open, double-blind, single-blind etc.) and the study configuration (parallel\cross-over design). In case of a double-blind trial, the parties of the study that will be blinded should be specified.

Since RCTs are the highest quality interventional study types, a thorough justification of not choosing an RCT in case of interventional studies should be provided. When choosing an RCT, it should be specified whether it is a standard or a pragmatic RCT and the rationale for choosing one of the two.

If observational, it should be specified if it is a descriptive study with no comparison between groups or if it is a cohort\case-control\cross-sectional study with comparison groups.

In this section it should be specified whether the study is cross-sectional or longitudinal, retrospective or prospective, mono- or multi-centric etc.

Thus, flow charts and a schematic diagram of the design are helpful.

Potential limitations of the study design, including issues relating to bias, and ways to reduce these limitations should be specified.

Study population

The study population has to be clearly identified and suitable for the study objectives.

⁹ E.g. on-going studies that don't fill all the gaps, on-going studies that don't respond to the research question etc. The eligibility criteria for AEG, including considerations on ongoing studies, can be found within EUnetHTA Criteria to select and prioritize health technologies for additional evidence generation. July 2012.

¹⁰ Please refer to WP7 SG2 Position paper on how to best formulate research recommendations. July 2015.

¹¹ Please refer to WP7 SG2 Position paper on how to decide on the appropriate study design. June 2015

Inclusion and exclusion criteria, based on a scientific rationale and used to screen\define the population, should be precisely listed. Inclusion criteria should define who will be eligible as a subject, while exclusion criteria will help further define the study population, excluding subjects not suitable or at particular risk from the study interventions or procedures (safety concerns, lack of suitability for the trial). The justification of criteria should be provided.

The occurrence of an event can be part of criteria used to screen/define the population.

Possible subgroups, defined as groups of subjects with specific needs by age (e.g. children, elderly), by gender or specific gender conditions (e.g. women of childbearing age, pregnant and breastfeeding women), subjects with rare and ultra-rare diseases or healthy volunteers or other specific subgroups should be described in this section, if needed.

It seems useful to report the flow chart of population selection and allocation.

If relevant, ethical considerations should be discussed.¹²

In this section, a description of risks and benefits related to the study population should be provided, if applicable. The risks and benefits of the study depend on who the participants are and the enrolment criteria must be constructed in a way to ensure an equitable selection of subjects; and to avoid risks for vulnerable subjects.

The risks might be avoided by subject monitoring, appropriate subject withdrawal criteria and follow-up.

This section should also address early withdrawal criteria to withdraw subjects from the study.

Intervention and comparator

This section provides more specific details about the study investigation (drug, device or procedure).

The treatment of each arm of the study should be described (including comparator, if any). Following information should be provided:

- identity (description of the product -drug, device, procedure-, approved indication and mechanism of action, if applicable)
- treatment regimen and justification of the choice (e.g. dose, route of administration for drugs, procedures and instructions for use in case of a medical device);
- prior and concomitant therapy (medication\ treatments permitted and not permitted before and\or during the trial).
- emergency treatment\ rescue medication, if any.

It should be also specified whether the investigational products and auxiliary products used in the study are authorised or not and, if authorised, whether they are to be used in accordance with the terms of their marketing authorisations.

If relevant, ethical considerations should be discussed.¹²

Study outcomes

The chosen outcomes have to reflect the study objective and be suitable to verify the study objective.

This section should provide a definition of the primary and secondary outcomes, if any, and the specific

¹² Ethical considerations related to the population, intervention and the choice of comparator are different from the ethical considerations referred to within the additional element "Ethics and protection of human subjects". Ethical aspects concerning the use of a technology without enough evidence or the ethics of choosing the comparator should be agreed upon by all partners, therefore these aspects are considered part of core elements. On the other hand, the ethical conduct of a study (protection of data, declaration of interest, informed consent to patients etc.) is related to the implementation of the study itself, thus considered "additional element".

parameters to be measured (kind of measurement, tools and time-point).

The temporal dimension must be incorporated in the definition of this criterion and a link to clinical relevance given. If a surrogate outcome and not a clinical outcome is used, it should be justified (e.g. by bibliographic reference, guidelines etc.).

If any of the assessment parameters is standard, i.e. widely used and generally accepted as reliable, the validity of the outcome measurement should be documented (e.g. relevance, precision, accuracy, specificity etc.). It may be helpful to describe rejected alternatives. Scale and questionnaires should be validated as well.

STATISTICAL ASPECTS

Sample size calculation

The definition of the study size should be defined and calculated on the basis of the primary outcome of the study, and it should be appropriate to show the treatment effect and its relevance.

This section should describe the number of subjects planned to be enrolled and needed to achieve the study objectives¹³ and how this was determined, the reason (clinical/statistical) for the choice of the sample size, including calculations of the statistical power of the study.

For a study intended to show a difference between treatments, the difference that the study aims to detect should be provided.

It should be evaluated if the study is feasible in terms of number of subjects involved.

Statistical analysis

In this section a description of all the statistical methods to be employed in the analysis of primary and secondary outcomes should be provided, including:

- the analysis sets for interventional studies: intention-to-treat, per protocol, per treatment;
- the level of significance to be used (p-value and/or confidence intervals):
- the selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects) and the reasons to exclude from the analysis patients for whom data are available
- definition of subgroups;
- procedures for accounting for missing, unused, and spurious data;
- timing/frequency of any planned interim analysis(es) and criteria for the termination of the trial earlier than planned (in which cases it should be stopped);
- any calculations that will be considered or performed to evaluate confounding variables, including any additional analyses (e.g. subgroup, stratified and adjusted analyses).

SETTING, DURATION AND FOLLOW-UP

This section provides an overview of the study timelines.

The expected overall length of the study should be stated (start and end date), and the periods of enrolment/recruitment, of treatment/exposure, of follow-up and data collection and analysis. Plans for base-line visits and follow up should be provided.

The study protocol should clearly indicate which outcomes will be measured at each follow-up (follow-up for adverse events and/or for efficacy and/or for effectiveness outcomes of the study).

¹³ How it is reported in the Seattle Children Hospital Guidelines for protocol writing: “A study that is not large enough to achieve the stated objectives is not considered scientifically valid. A study that is larger than necessary exposes more subjects to risk and inconvenience than required to achieve the scientific aims”.

- If an interventional trial is considered, the expected duration of subject participation (first patient enrolled- last patient completed) and a clear definition of the end of the clinical trial should be given. A description of the stopping rules or discontinuation criteria for individual subjects, specific parts of trial and entire trial should be provided.
- If an observational study is considered, the period of exposure should be described.
In observational studies, planned date for start/end of data collection should be specified.

It should also be evaluated if the study is feasible in terms of duration of follow-up.

BIBLIOGRAPHY

Numbered list of literature or electronic references of documents referred to in the protocol, including the reference to any existing protocol on the same topic (previously elaborated by other research organizations) and used to draft the core protocol.

1.3.3. “ADDITIONAL ELEMENTS”

General and administrative information

- Study\protocol title and study registration number (EU trial number/EU PAS register number), if existing.
- Protocol identifying number, given by the sponsor and specific for the version provided, if any.
- Date of validation of the current\provided version of the protocol.
- List of all main responsible parties and contacts, if any, including the sponsor (name and address), the monitor and the principal investigator (name, title, and the address and telephone number of the research site).
- Names and titles of people authorized to sign the protocol (i.e. scientific committees, if any).
- Locations involved in the study that is name(s) and address(es) of the structures and/or institutions involved in the study.

Study procedures and procedures to avoid bias

- Description of the recruitment and informed consent procedure.
- Procedures for the administration of intervention and the comparator to both subjects groups.
- Procedures for monitoring subject compliance.
- Methods and timing for assessing, measuring, recording, and analyzing of outcome parameters and covariates, including if local or central trial investigator assessment will be realized.
- Description of the procedures for ancillary tests, if any (biological materials to be used, storage, analytical tools, informed consent).
- Procedures taken to avoid bias, such as:
 - method for assigning subjects to treatment groups (method of randomization, if any; rules for maintaining the codes); method of generating the allocation sequence (e.g., computer-generated random numbers), mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes);
 - plan for blinding, how and who will be blinded after assignment to interventions (e.g., study participants, care providers, outcome assessors, data analysts), and rules for breaking the blind. If the study does not contemplate a randomization, it may still be useful to include the details for how measurements\tests will be blinded to interpretation;
 - possible confounding variables, effect modifiers to consider and efforts to address them.

Data management

- Description of sources of data used for the assessment of outcomes (clinical records, laboratory markers, claims data, self-report, interview including scales and questionnaire, etc.) and validation. If the study is based on secondary analysis of an already existing data source, such as electronic records or databases, any information on the validity of the data should be reported.
- Procedures and tools for data collection (paper-based, electronic case reporting forms etc.).
- Data analysis.
- Data storage (software, archive etc.).
- Data property in particular for multicentre studies.

Adverse events and safety monitoring

- Procedures for identification, recording and reporting adverse events and for follow-up of subjects after adverse reactions.
- Description of procedures relating to the withdrawal of subjects from treatment including procedures for replacement of subjects and the follow-up of subjects that have been withdrawn.
- Description of management of adverse events (guidance on treatment modification).

Administration of the study

- Identification of the recruitment centers and/or health professionals that have to be involved.

Quality Control and Quality Assurance

- Description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification and validation of outcomes, storage of records and archiving of the statistical programming performed to generate the results.
- In this section, it should be stated that the trial will be conducted following the protocol, Good Clinical Practice (for interventional studies) (ICH E6), and regulatory requirements.

Direct Access to Data and Monitoring

- System in place for independent review or audit.
- Statement from the sponsor confirming that the investigators and institutions involved in the study are to permit monitoring, audits and regulatory inspections, including provision of direct access to source data and documents.

Ethics and protection of human subjects

- Compliance with national and European Union requirements for ensuring the rights of participants.
- Description of requirements of Ethics Committee/ Institutional Review Board approval.
- Outcome of ethical review procedure.
- Informed Consent Forms (ICFs): the approved version of the protocol must have copies of ICF, both in English and the local language in which they are going to be administered, approved by the Ethics Committee. If the research involves more than one group of individuals, for example healthcare users and healthcare providers, a separate specifically tailored ICF must be included for each group. This ensures that each group of participants will get the information they need to make an informed decision.

Data Handling and Record Keeping

- Description of measures employed to guarantee protection of personal data.

Publication Policy

- Description of plans for communicating study results (progress reports and final reports) to regulatory authorities, sponsors, local investigators and participants to the study (only final report).
- Description of plans for disseminating study results (including publication) to scientific community and policy makers.

Financing and insurance

- Financing and insurance, if not addressed in a separate document, including a budget section (a detailed item-wise breakdown of the funds requested for, along with the justification for each item).

Project management

- Roles and responsibilities (sponsor and investigator).
- Curriculum Vitae of investigators.
- Declaration of competing interests.

1.4 Bibliography of the first section

1. Carbonneil C. et al. A common policy framework for evidence generation on promising health technologies. *International Journal of Technology Assessment in Health Care*, 25:Supplement 2 (2009), 56–67.
2. “Improving Additional Evidence Generation for health technologies”. Poster developed by The French National Authority for Health (HAS) for the EUnetHTA conference 2014.
3. REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
4. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH HARMONISED TRIPARTITE GUIDELINE:
 - ICH E8: General considerations for clinical trials, CPMP/ICH/291/95 (1997)
 - ICH E6: Good Clinical Practice: Consolidated guideline, CPMP/ICH/135/95 (1996) at <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html>
 - ICH E3: Structure and content of clinical study reports, CPMP/ICH/137/95 (1995).
5. European Medicines Agency (EMA) (2012). Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies. EMA/623947/2012
6. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). ENCePP checklist for study protocols at http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml
7. Seattle Children's Hospital Guidelines for protocol writing and templates at <https://www.seattlechildrens.org/doc/guidelines-for-protocol-writing.doc>

Other consultations:

8. CONSORT Checklist (Consolidated Standards of Reporting Trials), 2010
9. STROBE Checklist (The Strengthening the Reporting of Observational Studies in Epidemiology), 2007
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Partners' templates or documents for Additional Evidence Generation:

11. Research proposal of the core study, ZIN
<https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/pakket/werkwijze-pakketbeheer/voorwaardelijke-toelating/voorwaardelijke-toelating/voorwaardelijke-toelating/zinl%3Aparagraaf%5B6%5D/zinl%3Adocuments%5B2%5D/1505-formulier-voor-indienen-dossier/Formulier+voor+indienen+dossier.doc>.
12. Guide on post-authorization studies, HAS. «Les études post-inscription pour les technologies de santé (médicaments, dispositifs médicaux et actes), Modèle de protocole»
http://www.has-sante.fr/portail/upload/docs/application/pdf/2014-02/les_etudes_post-inscription_sur_les_technologies_de_sante_medicaments_dispositifs_medicaux_et_actes_modele_protocol_e_pi.pdf
13. Integrated Research Application System (IRAS), Integrated Dataset, NICE
<https://myresearchproject.org.uk/help/Help%20Documents/IRASIndex.pdf>
14. “Post-introduction Observation of Health Technologies. A methodological guideline” at <http://www.sergas.es/docs/Avalia-t/Post-introObs.pdf>

SECTION 2. PILOT ON RENAL DENERVATION – CORE PROTOCOL FOR AEG

The objective of the 2nd section of this pilot is to test the developed template, provided in Section 1, and the SG2 methodological papers about research recommendations and study design (WP7 SG2 Position paper on how to best formulate research recommendations and WP7 SG2 Position paper on how to decide on the appropriate study design).

It was decided to test the documents on a practical example of technology in need of AEG identified in an HTA report. The topic selection process is described in the Appendix 1. The technology used as example has been chosen on the basis of the existing HTA report¹⁴: Renal Denervation “Renal denervation systems for treatment-resistant hypertension”, EUnetHTA WP5 Strand B, 2nd pilot rapid assessment” (December 2013). The update of the report until December 2014 is shown in Appendix 2.

On the basis of the knowledge gaps arising from the HTA report and its update, the research question and the PICO for the chosen technology (renal denervation) were defined. This step has been elaborated following the process recommended in the WP7 SG2 Position paper on how to best formulate research recommendations:

- Establishing the *evidence profile* of the technology, i.e. the definition of all the assessment questions of interest to demonstrate safety and effectiveness of the technology. The evidence profile has been developed following the PICO format and the outcomes were subdivided according to the domain they belong to. The types of study designs to be included for each domain are also reported in the evidence profile.
- Comparing the *evidence profile* of the technology to the results of the HTA report and its update: results from the literature review have been transferred into the evidence profile and the quality of evidence has been stated (EUnetHTA methodological guidelines and GRADE were applied to assess the quality of evidence). Consequently, evidence\knowledge gaps were highlighted when there were no available or low quality data, allowing defining the research question for AEG.

Subsequently, the definition of the study design most suitable to answer that research question has been performed, on the basis of the WP7 SG2 Position paper on how to decide on the appropriate study design.

The process of defining the research question and study design is meant to be performed with all relevant stakeholders at an early stage, as indicated in WP7 SG2 Position papers. Given the time limits for this pilot, stakeholders were involved via consultations.

Finally, on the basis of the proposed template for AEG (provided in section 1), the current Core protocol for AEG on renal denervation was developed. EUnetHTA JA1 WP5 methodological guidelines¹⁵ have been also consulted for the definition of outcomes.

In this section, only the elements of the **Core protocol template for AEG** are presented. Furthermore, the core elements have been filled-in only with information deducible from the HTA report or its update (our only source of information in this pilot); thus some items of the core elements are left empty, as they require the involvement of additional expertise (and additional source of information).

¹⁴ This report is a Rapid Relative Effectiveness Assessment developed using HTA Core Model within EUnetHTA.

¹⁵ Guidelines on methodological issues that are encountered while performing a rapid REA (relative effectiveness assessment) of pharmaceuticals.

Core protocol for AEG for renal denervation

TITLE

Core protocol for AEG on renal denervation systems for treatment-resistant hypertension

SYNOPSIS

Title	Core protocol for AEG on renal denervation systems for treatment-resistant hypertension
Study design	Multi-center, prospective, single-blind, randomized, controlled study
Target population	Patients with treatment-resistant hypertension
Intervention	Catheter-based renal denervation and conventional optimal medical therapy
Comparator	Sham treatment and conventional optimal medical therapy
Outcome(s)	Difference in ambulatory systolic BP (24 h-measured) reduction from baseline to 6 months between the RDN and the control group
Sample size	420 subjects
Time frame	6 months for the primary outcome. 2 years for extended follow-up.

STUDY BACKGROUND

Hypertension

The target population involves patients with treatment-resistant hypertension, a condition for which conventional treatments are inadequate in treating a patient's hypertension (patient's blood pressure is resistant to conventional drugs).

The current standard treatment is based primarily on pharmacological treatment (antihypertensive drugs) and lifestyle modifications (for example reduction of sodium intake or weight loss). Resistant-hypertension (RH) is thus defined as blood pressure (BP) not reaching the guideline target values (that is a BP $\geq 140/90$ mmHg) in presence of three or more antihypertensive drugs (including a diuretic) of different classes at maximal or highest tolerated dose (Mahfoud, 2013) and despite lifestyle modifications.

The possibility of a secondary cause of hypertension, such as primary hyperaldosteronism, renal artery stenosis, pheochromocytoma, sleep apnoea syndrome, should always be considered and must be ruled out (Mancia, 2013, Mahfoud, 2013). Furthermore apparent or pseudo-resistant hypertension has to be excluded and can be defined as the failure in obtaining an adequate BP caused by:

- improper BP measurement technique,
- by the elevation of office BP due to a persistent alerting reaction to the BP-measuring procedure (white-coat effect),
- by the non-adherence to the prescribed treatment regimen (lifelong and mainly asymptomatic disease) (Mancia, 2013).

Resistant-hypertension is associated with an increased-risk of cardiovascular events (Mahfoud 2013, Mancia 2013, Vasan 2001). Hypertension will, if untreated, increase the risk of e.g. cardiovascular disease, stroke and renal failure.

Patients commonly have associated cardiovascular risk factors such as diabetes, obstructive sleep apnoea, left ventricular hypertrophy, which impair the prognosis (Calhoun, 2008).

Normally, the patient does not experience symptoms that are associated with resistant hypertension (EUnetHTA report).

The exact prevalence of resistant hypertension is unknown (Calhoun, 2008). The ESH and the ESC report that, depending on the population examined and the level of medical screening, the prevalence of resistant hypertension has been reported to range from 5–30 % of the overall hypertensive population, but probably less than 10 % (Mancia, 2013). The prevalence of hypertension (all cases) is estimated to be approximately 30–45 % of the general population (Bhatt, 2014).

Renal denervation (RDN)

Catheter-based renal denervation is an accepted alternative non-drug-approach to treat RH. The procedure involves the destruction of afferent and efferent sympathetic nerves travelling along the wall of the renal arteries, which may cause reduction in BP.

The rationale of this approach relies on the impact of sympathetic influence on blood pressure control. Renal afferent nerves contribute to central blood pressure elevation by stimulating CNS (solitary tract and nucleus), while efferent nerves innervate renal vasculature and enhance sodium and water retention, renin release and control renal blood flow (EUnetHTA report; Mahfoud, 2013).

In particular, the denervation systems act by increasing temperature in a limited area of the artery wall, and thus ablating both sympathetic afferent and efferent fibers, which lay within the wall of the artery and course along it.

Most RDN systems use radiofrequency energy (Symplicity®, OneShot™, EnligHTN™, Vessix™ V2, Iberis™, Marinr® and ThermoCool®), however the PARADISE™ system uses ultrasonography.

Renal denervation is aimed at improving BP control in patients whose BP is resistant to conventional drug therapy (EUnetHTA report).

According to the ESH and the ESC guidelines, indeed, it is recommended that renal denervation is restricted to resistant hypertensive patients who are at particularly high risk, after documenting the inefficacy of additional antihypertensive drugs to achieve BP control (Mancia, 2013).

On the basis of the ESC consensus (Mahfoud, 2013), patients are eligible to renal denervation if they have severe RH and should meet a set of criteria (see inclusion criteria in “Study population” section) before renal denervation is considered. In particular, before considering renal denervation, patients should have been evaluated by a hypertension expert in specialized centres where optimization of the antihypertensive drug treatment as well as the identification of contributing lifestyle factors should be part of the practice. Pseudo resistance and secondary causes of hypertension must be also ruled out.

Evidence profile

Information on renal denervation needed/required to demonstrate the rationale for its intended clinical use and its safety and effectiveness profile, the evidence profile, is presented in Table 1.

As the scoping carried out by HTA reports' developers contributes to the definition of the rationale supporting technologies' potential clinical role, this profile has been defined on the basis of the HTA report on renal denervation¹⁶.

¹⁶ “Renal denervation systems for treatment-resistant hypertension”, EUnetHTA WP5 Strand B, 2nd pilot rapid assessment” (December 2013).

Table 1. Evidence profile for renal denervation

RATIONALE		
Renal denervation (destruction of sympathetic nerves in the wall of renal arteries) as add-on therapy to standard of care can be a safe and effective alternative to treat patients resistant to conventional therapy.		
INDICATION: treatment of treatment-resistant hypertension		
POPULATION	Patients with treatment-resistant hypertension with blood pressure \geq 140/90 mmHg and without secondary cause of hypertension.	
INTERVENTION	Renal nerve ablation and denervation	
COMPARATOR	Standard of care	
DOMAIN	OUTCOME	STUDIES INCLUDED
SAFETY	Total adverse events (in % of patients) Major adverse events (in % of patients)	RCTs CTs Prospective case series (not necessary comparative)
EFFECTIVENESS	Overall mortality Cardiovascular mortality Cardiovascular morbidity Blood pressure changes Left ventricular hypertrophy and change in ejection fraction Kidney function Effect on daily living (exercise) Quality of life and patient satisfaction Decrease in number of medications	SRs/HTAs RCTs Prospective CTs (only if data from RCTs were lacking or insufficient)

Literature overview - based on EUnetHTA report¹⁷ and update (appendix 2)

- Efficacy\Effectiveness

Most of the studies evaluate the changes in blood pressure as primary efficacy\effectiveness outcome.

Renal denervation, using Symplicity catheter, appears to decrease BP, especially if compared with baseline BP (Symplicity HTN-1 Investigators, 2011; Symplicity HTN-2 Investigators, 2010; Bhatt, 2014), whereas the effect of other denervation systems is still uncertain. However, overall, contrasting evidence on BP changes is emerging from recent studies.

The two most recent systematic reviews (SRs) that examined changes in BP (Davis, 2013; Pancholy, 2014) report that renal denervation resulted in a significant decrease in systolic blood pressure (SBP) and diastolic blood pressure (DBP) when compared with the control group, thus favouring renal denervation (significant mean difference). The quality of the evidence was low and very low, respectively.

The most recent blinded-RCT (Bhatt, 2014) with the highest number of participants (535 patients), HTN-3 trial, showed a non-significant between-group difference (RDN and control group) in the change in office and ambulatory blood pressure at 6 months (between-group difference: -2.39 mmHg, $p=0.26$). The quality of this evidence was moderate. It has to be noted that the effect of renal denervation was not significant between-groups, but if considering only non-african American patients, renal denervation imparted\caused a statistically significant reduction in systolic BP compared with control ($p=0.012$). On the contrary, African American patients showed a significant BP reduction even if treated with sham treatment.

One recent not-blinded RCT (Fadl Elmula, 2014) with small sample size (19 patients) and comparing RDN versus clinical drug adjustment concluded that BP control through 6 months by drug adjustment was superior to renal denervation. The quality of this evidence was low.

Other studies showed a significant decrease of BP from baseline to 6 months (Hering, 2014) and reported non-significant changes in the control group, without reporting a between-group comparison. The quality of the evidence was very low.

Some experts report that confounding variables which could influence the results of the studies on BP reduction (which could have in particular influenced the HTN-3 results) and that should be addressed in future studies are: the issue of stabilized medication regimens before and during the study period to avoid confounded blood pressure assessments, the adequate experience of hypertension specialists within recruiting centres and the correctness of technique used to perform the ablation.

Some studies evaluating this outcome are on-going.¹⁸

There is no evidence regarding overall mortality and cardiovascular mortality (no published or on-going study with mortality as primary efficacy outcome).

There is not enough evidence on cardiovascular morbidity (stroke, myocardial infarction, heart failure): only one on-going study with 6 patients assesses this outcome (onset or progression of cardiovascular disease).

Left ventricular hypertrophy was assessed in four published studies and three of them reported less hypertrophy in patients who underwent RDN (Brandt, 2012b; Pokushalow, 2012; Mahfoud, 2013b; Mahfoud, 2014). It should be specified that left ventricular mass was measured differently in the analysed studies and the quality of the studies was very low. Two on-going studies assess the cardiac function.

Only one RCT (Symplicity HTN-2 Investigators, 2010) assessed kidney function as outcome. According to the study, there was no change in kidney function, based on eGFR and creatinine levels, following renal denervation

¹⁷ "Renal denervation systems for treatment-resistant hypertension, EUnetHTA WP5 Strand B, 2nd pilot rapid assessment" (December 2013)

¹⁸ It has to be noted that, within the ongoing trials database, it is not possible to obtain all details of the study, some of which could affect the outcome (such as the selection of patients by specialized centres, optimization of the drug therapy prior to randomization and the monitoring of the adherence).

at the 6-month follow-up, but no definitive conclusion could be drawn, because the quality of the evidence was low.

Only two studies (Ukena, 2011; Ewen, 2014) evaluated changes in activities of daily living but the quality of evidence is very low. No on-going study is evaluating this outcome.

There is no evidence that the number of antihypertensive medication decreases following RDN. One SR (Gosain, 2013) assessed this outcome and reported results narratively. EUnetHTA report stated that, although data from nine studies including 430 patients in total may suggest a decrease in number of anti-hypertensive medications following renal denervation, no conclusion could be drawn.

So far, no evidence was found on how RDN affects outcomes such as quality of life and patient satisfaction in published or on-going studies.

- Safety

Overall, safety profile of RDN suggests it is a safe procedure in the short to medium term.

However, due to methodological limitations of the studies, no firm conclusion can be drawn:

- In many studies safety is not considered as the main outcome, often the reported complications or the adverse events are not pre-defined and it is likely that some complications were not adequately reported.

In two of the RCTs (Ukena, 2011; Pokushalov, 2012), all non-RCTs (Mahfoud, 2011; Mahfoud, 2012; Brandt, 2012) and many case series, safety was not considered as the main outcome, and complications and adverse events were incompletely reported (Voskuil, 2011; Brinkmann, 2012; Hering, 2012; Ukena, 2012; Zuern, 2012; Prochnau, 2012; Fontenla, 2013; Kaltehbach, 2013). Often, the authors referred to the non-existence of severe/major procedure-related complications or adverse events without defining a 'severe adverse event'.

Except for HTN-3 trial, in which the primary safety outcome was clearly stated, even in the updated studies safety was not the main outcome. In one RCT (Fadl Elmula, 2014) safety outcomes were not pre-specified and in two CTs (Hering, 2013 and 2014) the authors report the non-occurrence of adverse events related to the procedures in the treated patients, without defining which were the adverse events.

- There is no evidence about long-term safety.
Lack of knowledge about long-term occurrence of adverse effects (even the update-studies have follow-up of maximum 12 months).
- Possibility of bias due to lack of blinding and small sample size: limit partially solved with HTN-3 trial. This RCT clearly specified the safety outcome and reported that the safety performance criterion was significantly met.

In general, the quality of safety evidence was rated from moderate to very low.

It has to be specified that most of the evidence and experience is related to the Simplicity system (all the update-studies involve Simplicity® catheter). Other RDN systems are currently being implemented, which might differ in terms of mechanism and size, and might thus have a different safety-efficacy profile.

The available evidence presented here has been matched with the evidence profile, in order to highlight existing evidence gaps (Table 2).

Table 2. Summary of the available evidence (EUnetHTA report and update) against the Evidence Profile

DOMAIN	OUTCOME	STUDIES INCLUDED	QUALITY OF EVIDENCE (GRADE) (high/moderate/low/very low)
<u>SAFETY</u> (RCTs, CTs, prospective case series) observational)	Total adverse events (in % of patients)	<u>EUnetHTA report:</u> 3 RCTs 3 CTs 18 observational studies 3 ongoing studies	LOW LOW VERY LOW
		<u>Update:</u> 1 SR (Pancholy, 2014) 1 RCT (Fadl Elmula, 2014) 2 CTs (Hering, 2014, Hering, 2013) 3 ongoing studies	LOW MODERATE VERY LOW
	Major adverse events (in % of patients)	<u>EUnetHTA report:</u> 4 RCTs 3 CTs 18 observational studies 2 ongoing studies	LOW LOW VERY LOW
		<u>Update:</u> 1 SR (Pancholy, 2014) 1 RCT (Fadl Elmula, 2014) 2 CTs (Hering, 2014, Hering, 2013) 3 ongoing studies	LOW MODERATE VERY LOW
<u>EFFECTIVENESS</u> (SRs/HTAs, RCTs, prospective CTs (only if data from RCTs were lacking or insufficient))	Overall mortality	<u>EUnetHTA report:</u> 1 SR (Davis, 2013) Any ongoing study	Assessed narratively as no change
		<u>Update:</u> NO STUDIES Any ongoing study	\
	Cardiovascular mortality	<u>EUnetHTA report:</u>	

		NO STUDIES (no SR, RCT or CT) <i>Any ongoing study</i>	\
		<u>Update:</u> NO STUDIES <i>Any ongoing study (except for 2 which reported death and cardiovascular accident as safety outcome)</i>	\
	Cardiovascular morbidity (stroke, myocardial infarction, HF)	<u>EUnetHTA report:</u> 1 SR (Andersson 2013, failing to identify any studies)→ NO STUDIES <i>Any ongoing study</i>	\
		<u>Update:</u> NO STUDIES <i>1 ongoing study (Onset or progression of cardiovascular disease), 2 studies which reported myocardial infarction as safety outcome</i>	\
	Blood pressure changes	<u>EUnetHTA report:</u> 2 SR (Davis 2013, Gosain 2013) 1 HTA (Andersson 2013) 1 RCT (Ahmed 2012) <i>22 ongoing studies</i>	From VERY LOW to MODERATE*
		<u>Update:</u> 1 SR (Pancholy, 2014) including 3 RCTs and 2 CTs 1 HTA (MUHC, 2013) 2 RCTs (Bhatt, 2014 HTN-3, Fadl Elmula, 2014) 4 CTs (Hering, 2014 and 2013, Ewen, 2014, Mahfoud, 2014) <i>6 ongoing studies</i>	From VERY LOW to LOW**
	Left ventricular hypertrophy and change in ejection fraction	<u>EUnetHTA report:</u> 1 HTA (Andersson 2013) including one non-RCT (Brandt, 2012b) 1 RCT (Pokushalow 2012) 1 CT (Mahfoud 2013b) <i>Any ongoing study</i>	VERY LOW VERY LOW VERY LOW
		<u>Update:</u>	

		1 CT (Mahfoud, 2014) 2 ongoing study	VERY LOW
	Kidney function	<u>EUnetHTA report:</u> 1 SR (Gosain 2013) identified 1 RCT (Esler, 2010 HTN-2) 1 ongoing study (RCT)	LOW
		<u>Update:</u> NO STUDIES Any ongoing study	\
	Effect on daily living (exercise)	<u>EUnetHTA report:</u> 1 RCT (Ukena 2011) Exercise capacity reported as maximum work load and peak oxygen uptake (VO2peak). Any ongoing study	VERY LOW
		<u>Update:</u> 1 CT (Ewen, 2014) Exercise capacity measured by workload and exercise time Any ongoing study	VERY LOW
	Quality of life and patient satisfaction	<u>EUnetHTA report:</u> NO STUDIES (no SR, RCT or CT) Any ongoing study	\
		<u>Update:</u> NO STUDIES Any ongoing study	\
	Decrease in number of medications	<u>EUnetHTA report:</u> 1 SR (Gosain 2013) Any ongoing study	Assessed narratively as No change
		<u>Update:</u> NO STUDIES Any ongoing study	\

*Only Davis, 2013 evaluated with GRADE

**GRADE was applied to Pancholy, 2014, Fadl Elmula, 2014, Hering, 2014

RATIONALE OF THE STUDY

From literature overview it emerges that RDN seems to be safe in the short to medium term, as reported by the EUnetHTA report and confirmed by the recent HTN-3 study, which reported that safety performance criterion was significantly met. On the contrary, the comparison of the evidence profile and the available evidence (Table 2) shows that there is still a need for further research on the effectiveness of renal denervation in RH versus optimal medical therapy.

With regards to effectiveness outcomes, assessing mortality and cardiovascular morbidity is important to directly evaluate cardiovascular risk reduction for patients with resistant hypertension, and represents an unmet need. It is true that for these outcomes the evidence is currently absent or too little, respectively, however their assessment would require a large scale and long-term study. Indeed, EMA 2013 states that “positive effects on mortality and cardiovascular morbidity can only be evaluated properly in large scale and long-term studies”. Taking into consideration BP reduction outcome and looking at the available evidence, it can be observed that previous low quality studies seemed to demonstrate a BP reduction, while the recent moderate quality study (HTN-3) failed to demonstrate the primary efficacy outcome of BP reduction.

BP reduction is usually accepted as a surrogate outcome for fatal and nonfatal cardiovascular disease (EUnetHTA guidelines for clinical endpoint¹⁹). Furthermore BP reduction has been associated with a reduction of the risk of cardiovascular death (Fornell 2013, Whelton 2002, Lewington 2002, Rosendorff 2007). Although caution should be taken, it is reasonable to state that significant BP reduction could reduce both morbidity and mortality from hypertension-caused diseases.

Thus, BP reduction could represent an acceptable surrogate outcome to assess the effectiveness of renal denervation.

In addition, this outcome would require a shorter-term follow up study compared to a long-term study necessary to assess mortality.

Finally, considering the existing evidence gaps on this technology and the urgent need to fill them, blood pressure reduction following RDN compared to medical therapy has been selected as the first outcome. The choice of this outcome for our research recommendation was shared and discussed with a small panel of experts in the field and this proposal has to be surely confirmed by a larger panel of experts²⁰.

It has to be noted that there are four on-going studies evaluating this outcome. However, some details of these studies (such as the selection of patients in hypertension specialized centres, the optimization of the drug therapy prior to randomization, the monitoring of the adherence), which could have an impact on the outcome\results and which should be better investigated, cannot be obtained from the on-going trials database (source of information for this pilot). More details are required to clearly define if these on-going studies could answer the evidence gap identified in this research recommendation and to state if the results of these studies should be awaited.

In this scenario, overcoming the limitations of previous studies, especially HTN-3 trial, which was the most recent rigorous trial on renal denervation so far, seems to be necessary.

Consequently, the current study may help collecting the additional evidence needed in order to fill an evidence gap on renal denervation, bypassing some limitations of the currently published studies, and may contribute to the decision-process of adoption of this technology.

¹⁹ “Some examples of surrogate endpoints are blood pressure as a surrogate endpoint for cardiovascular disease” EUnetHTA Guideline

²⁰ One EUnetHTA partners disagreed with the proposed outcome.

RESEARCH QUESTION

The primary objective is to evaluate the effectiveness of renal denervation (RDN) in reducing blood pressure compared to optimal medical therapy in patients with treatment-resistant hypertension.

EVIDENCE	POPULATION	INTERVENTION	COMPARATOR	OUTCOME (S)
-Generally low quality studies -Inconsistent results of recent literature	Patients with treatment-resistant hypertension	Renal denervation and conventional optimal medical therapy	Sham treatment and conventional optimal medical therapy	BP reduction ²¹

RESEARCH METHODS

Study design

On the basis of the evidence profile and the arising research question, the most appropriate study design to answer the question related to clinical effectiveness of the technology is an RCT. Thus, a multi-center, prospective, single blind, randomized, controlled study of the effectiveness of renal denervation compared to optimal medical therapy is suggested.

However the decision and its details should be supported by the opinion of experts and should involve consultation with guidance producers and trialists as suggested by the WP7 SG2 Position paper on how to decide on the appropriate study design.

Additional expertise and advice are required for describing details about blinding and way of randomization; filling-in these items is beyond the scope of this exercise.

Study population

Patients with treatment resistant hypertension.

According to the current accepted definition by ESC 2013 (Mancia, 2013) “hypertension is defined as resistant to treatment when a therapeutic strategy that includes appropriate lifestyle measures plus a diuretic and two other antihypertensive drugs belonging to different classes at adequate doses (but not necessarily including a mineralcorticoid receptor antagonist) fails to lower SBP and DBP values to < 140 and 90 mmHg, respectively”.

In particular, before considering renal denervation, thus before randomization, patients should be evaluated by hypertension experts in specialized centres and optimization and stabilization of the antihypertensive drug treatment as well as the identification of contributing lifestyle factors should be achieved as part of the practice.

Inclusion criteria

As stated in an expert consensus document on catheter-based renal denervation that was published in 2013 by the European Society of Cardiology (Mahfoud, 2013) patients should meet a set of criteria before renal denervation is considered, as follows:

²¹ Please see the rationale on the previous page.

- office-based systolic BP ≥ 160 mmHg (≥ 150 mmHg diabetes type 2) despite the use of ≥ 3 antihypertensive drugs in adequate dosage and combination (incl. Diuretic);
- treatment-resistance to lifestyle modification when changes in lifestyle fails to alter the BP (low sodium intake diet, weight loss...);
- exclusion of secondary hypertension (such as renal artery stenosis, pheochromocytoma, sleep apnoea syndrome, primary hyperaldosteronism);
- exclusion of pseudo-resistance using ambulatory BP (average BP > 130 mmHg or mean daytime BP > 135 mmHg);
- preserved renal function (GFR ≥ 45 ml/min/1.73 m²);
- eligible renal arteries in terms of length, diameter and morphology: no polar or accessory arteries, no renal artery stenosis and no prior revascularization.

Furthermore (reported in the HTN-3 study):

- age ≥ 18 and ≤ 80 years
- written informed consent.

Exclusion criteria

Described contraindications of RDN are:

- history of prior renal artery intervention including balloon angioplasty or stenting;
- evidence of renal artery atherosclerosis (defined as renal artery stenosis $> 50\%$) or renal artery aneurysm in either renal artery;
- presence of multiple main renal arteries in the kidneys or main renal arteries < 4 mm in diameter or < 20 mm in length;
- patients should be in stable clinical condition, thus ruling out patients with recent myocardial infarction, unstable angina pectoris or a cerebrovascular accident within the past 3–6 months .

Description of subgroups, of risks and benefits to subjects, early withdrawal criteria as well as further ethical considerations all require additional expertise, and are therefore out of scope of this exercise.

Intervention and comparator

Intervention

Catheter-based renal denervation added to conventional optimal medical therapy²².

Renal denervation is a treatment approved for treatment-resistant hypertension that uses low-level radio frequency energy or ultrasonography (depending on the device) to disrupt renal sympathetic nerves and deactivate hyperactive nerves. Most systems are catheter-based and the catheter is introduced through the femoral artery and threaded into the renal artery lumen. Subsequently, the energy is delivered to ablate the sympathetic nerves. Since there are different RDN systems, there could be slight differences in related procedures. Furthermore, there could be different concentration of nerves along the renal artery, thus the ablation should be done throughout the course of the artery, and if necessary, more than once to ensure a sufficient and proper ablation.

As a consequence, a precise procedure needs to be established to ensure a standardized method.

²² We did not limit the study to a specific type of catheter: possibility to investigate other than Simplicity catheter, since many systems are currently being implemented and most of the current evidence is related to the Simplicity catheter.

Renal denervation is intended to be add-on therapy to pharmaceutical treatment.

Details about emergency treatment needs to be further discussed with experts and are out of scope of this exercise.

Ethical considerations about the use of the technology will need additional expertise and are out of scope for this exercise.

Of all renal denervation systems, the Symplicity[®], OneShot^{™23}, EnligHTN[™], Vessix[™] V2 and Iberis[™] systems are CE-marked in Europe. None of the systems is FDA-approved, but all are seeking such status. Of the ultrasonography devices that are in development, only the PARADISE[™] system (ReCor Medical) has received the CE mark.

Renal denervation is used in this study in accordance with its approved indication, i.e. resistant hypertension (Mahfoud, 2013).

Comparator

Sham treatment²⁴ and conventional optimal medical therapy.

The Task Force for the management of arterial hypertension of the ESH and the ESC (Mancia, 2013) describe in their guideline that most patients with resistant hypertension require the administration of more than three drugs. In current practice this combination of drugs exists: thiazide diuretic, a long-acting calcium channel blocker, an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, and a beta-blocker in patients younger than 60 years of age (CADTH 2013).

Rationale for sham treatment:

- it was already used by the approved American study (HTN-3 study) that failed its primary efficacy outcome;
- a hypothesis is that the sham-treatment may have increased the adherence to drug therapy;
- safety of the sham treatment evaluated through the absolute rate of major adverse events: one major adverse event in the sham-procedure group (0.6%) (HTN-3 study, Bhatt 2014);
- furthermore, in HTN-3 study, major adverse events demonstrated to be not significantly different between groups: “there were few major adverse events in the trial: five in the denervation group (1.4%) and one in the sham-procedure group (0.6%), for a difference of 0.8 percentage points (95% CI, -0.9 to 2.5; P = 0.67)”.

Blinding could have an impact (this could be one of the explanations of the failure of the HTN-3 study).

We suggest to perform the monitoring of the adherence to drugs intake²⁵ and to diet in both study groups during

²³ Withdrawn from the market in december 2014.

²⁴ The HTN-3 study revealed that an important placebo effect was present in the control group. “Perhaps this placebo effect was accentuated by the use of an invasive procedure in the control group (i.e., a femoral-artery puncture and renal angiography), which may have increased adherence to medication and diet. Regardless, this finding has important therapeutic implications for the design of trials of antihypertensive (and other) medications, devices, and strategies” (Bhatt, 2014). “SYMPPLICITY HTN-3, which with 535 patients represents the only major randomized study to date, demonstrated significant ($P < .001$) — though nearly identical — drops in office systolic BP between baseline and 6 months for the treatment (-14.13 ± 23.93 mm Hg) and control groups (-11.74 ± 25.94 mm Hg; $P = .26$). This demonstrates the value of having a sham control. If it were only the denervation arm, it would have been a positive trial” (interview to Bhatt).

²⁵ A limitation of the HTN-3 trial was that medication adherence could not be confirmed (urine level of antihypertensive medications).

the study period (urine level measurement, witnessed intake or questionnaires).

Monitoring the adherence to the antihypertensive therapy and to diet, as well as the use of the sham treatment, seems to be relevant factors to avoid confounders.

Further ethical considerations will need additional expertise and are out of scope of this exercise.

Study outcomes

- Primary outcome:

Difference in ambulatory systolic BP (24 h-measured) reduction²⁶ from baseline to 6 months between the RDN and the control group. The between-groups difference would be clinically significant if reduction was of at least 5 mm Hg²⁷.

BP is generally accepted as a surrogate outcome for cardiovascular disease (EUnetHTA guidelines; Mahfoud, 2013) and widely used, as explained in the above rationale (please see the item “rationale of the study”).

- Secondary study outcomes:

Effectiveness

- Difference in ambulatory diastolic BP (24 h-measured) reduction from baseline to 6, 12, 18, 24 months between the RDN and the control group
- Difference in systolic and diastolic BP (office-measured) reduction from baseline to 6, 12, 18, 24 months between the RDN and the control group
- Difference in ambulatory systolic BP (24 h-measured) reduction from baseline to 12, 18, 24 months between the RDN and the control group
- Change in heart rate (HR)
- All-cause\overall mortality at 2 year
- Cardiovascular mortality
- Cardiovascular morbidity (stroke, myocardial infarction and heart failure)
- Change in left ventricular mass (for left ventricular hypertrophy)
- Effect on body functions (kidney function)
- Effect on activities of daily living (BP during physical exercise)
- Decrease in number of medications
- Quality of life and patients satisfaction

Tools to be used to measure outcomes have to be discussed with experts, and are out of scope of this exercise.

Safety

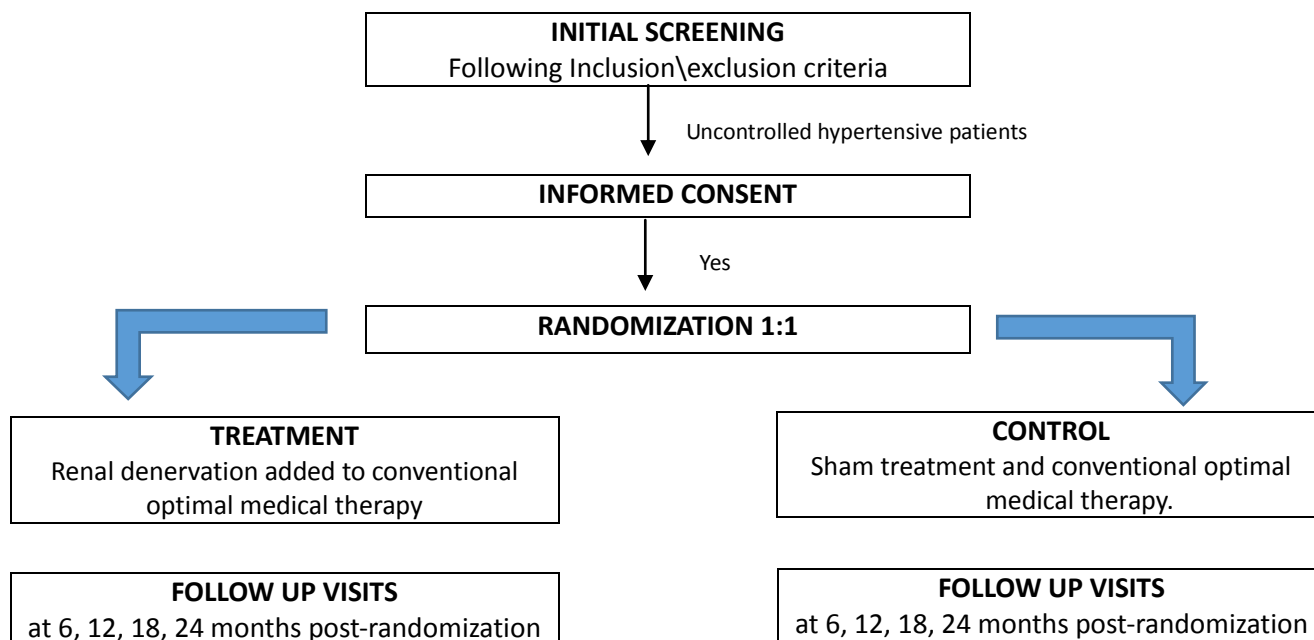
Recording of:

- Adverse events related to the procedures: intervention-related mortality, renal artery perforation\dissection and vascular complications (such as local hematoma, pseudoaneurysm) requiring intervention, bradycardia and hypotensive events.
- Adverse events during follow-up: hypotensive and hypertensive episodes requiring hospitalization, new renal artery stenosis >70% confirmed by angiography within 6 months of randomization, progress of renal disease (eGFR < 15 mL/min/m² or need for renal replacement therapy).

²⁶ The major advantage of out-of-office BP monitoring is that it provides a large number of BP measurements away from the medical environment, which represents a more reliable assessment of actual BP than office BP (Mancia, 2013).

²⁷ This clinically meaningful value is supported by literature (Bhatt, 2014; Whelton, 2002) and confirmed by a small group of clinicians. If necessary, it may be confirmed by a larger group of experts.

The proposed flowchart of the study is:



STATISTICAL ASPECTS

It is noteworthy that this core element could not be filled-in with the information deduced from the HTA report, but it required the involvement of additional expertise (clinicians and statisticians). The proposed clinically meaningful difference was done on the basis of literature references (Bhatt, 2014; Whelton, 2002) and confirmed by a small panel of experts. In the prospective of a European multicentric study, this proposal has to be surely confirmed by a larger panel of experts.

The suggested trial is a multicenter RCT single-blinded two-arm study designed to evaluate the effectiveness of renal denervation in the treatment of uncontrolled hypertension. The suggested primary effectiveness outcome of this trial is the mean change in ambulatory systolic blood pressure (SBP) from baseline to 6 months in the denervation group as compared with the mean change in the control group.

If the primary outcome is met, then a major secondary outcome, the change in office-based systolic and diastolic blood pressure from baseline to 6 months, will be tested.

We suggest inserting in the study no more than 3 of the next secondary study outcomes. Note that secondary outcomes are exploratory and must be interpreted with caution. Secondary analysis should be used only to support the primary outcome or to suggest working hypothesis.

Sample size calculation

The null and alternative superiority for the primary effectiveness outcome are:

H0: $\mu_T - \mu_C \leq 5$ mmHg

vs.

HA: $\mu_T - \mu_C > 5$ mmHg

where μ_T and μ_C are the mean reductions in SBP, from baseline to 6 months, for the denervation group and the control group, respectively, and 5 mmHg is a clinically meaningful difference between groups²⁸.

Assuming a 15 mmHg standard deviation of the Ambulatory SBP change per group (Ahmed, 2012) then an equal sample size of 382 subjects (191 for the denervation group and 191 for the control one) yields 90% power to demonstrate a > 5 mmHg difference between groups at a two-sided 0.05 level of significance. A two sample unpaired t-test was used for the sample size calculation for the primary effectiveness outcome hypothesis.

To account for approximately 10% rate of premature withdrawal or failure to obtain the primary outcome measure, 420 patients should be randomized in the two groups.

Statistical analysis

All statistical analysis will be performed using SAS or other widely accepted statistical software.

Descriptive statistics of continuous variables will be presented by arm and include sample size, mean, median, standard deviation, minimum and maximum. For categorical variables, the number and percentage of patients in each category will be presented by arm.

The intent-to-treat principle (all randomized patients) will be applied as primary analysis of the effectiveness endpoint.

The primary effectiveness analysis will be a two-sample t-test at a two-sided 0,05 level of significance. In addition, two-sided 95% confidence intervals will be presented.

Considering HTN-3 results, it would be interesting to plan a subgroup analysis by race. Nevertheless, description of subgroups and subgroups analysis, procedures for missing data, timing of any interim analysis (if necessary) is out of scope of this exercise.

SETTING, DURATION AND FOLLOW-UP

Patients are referred to centers specialized in the management of hypertension, in order to select patients with true resistant hypertension and avoid the recruitment of patients with “curable” forms of hypertension.

The procedure can be performed by an interventional cardiologist or radiologist and angiologist (Mahfoud, 2013), who is trained in the therapy and qualified to manage potential complications, such as acute dissection of renal arteries by stent implantation (EUnetHTA report).

Patients are followed for 2 years and blood pressure measurements are performed at baseline and after each 6 months.

Additional expertise is required for describing expected overall length of the study (start and end date), the periods of enrolment, of treatment, and data collection\analysis, the plans for base-line visits and follow up; filling these items is out of scope of this exercise, as well as the description of the stopping rules or discontinuation criteria for individual subjects, specific parts of trial and entire trial.

²⁸ This clinically meaningful value is supported by literature (Bhatt, 2014; Whelton, 2002) and confirmed by clinicians.

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APPENDIX 1

Topic selection process

The second part of the Core protocol pilot for AEG consists in testing the developed protocol template on a practical example. The candidate technology has been chosen through the topic selection process involving both WP7 SG2 partners and WP7 SAG.

In the first round (February-March 2014), WP7 SG2 partners and SAG were asked to

- notify technologies of interest for the pilot (technologies for which critical evidence gaps have been identified at the moment of a first HTA)
- and provide feedback on criteria for the topic selection,

through a topic selection form.

Seventeen technologies were proposed by WP7 SG2 partners, among which HAS and the authoring agencies made the first selection, leaving out candidates that were found not suitable for the pilot (technologies premature for an Additional Data Collection (ADC), for which the impact of ADC was not clear or for which there were many ongoing studies reported²⁹).

Ten technologies were proposed to WP7 SG2 partners for voting in the second round in May 2014. As no clear winner came out, the final choice has been made in July 2014 by the authoring agencies and HAS among three technologies that scored the same number of points in the second round: the **Circulite Synergy System** for chronic heart failure.

Several issues were encountered upon the start of the development of the protocol with the selected technology, which pointed to the need to reconsider the choice of topic. Such issues included: probable withdrawal of CE mark; too much missing evidence identified; inability to get in contact with the manufacturer. Keeping such issues in mind, WP7 SG2 partners agreed at the 3rd Face to Face meeting in November 2014 to change the topic and produce the pilot for Renal denervation systems for treatment-resistant hypertension, based on EUnetHTA WP5 Strand B, 2nd pilot rapid assessment.

²⁹ According to EUnetHTA Criteria to select and prioritize health technologies for additional evidence generation. July 2012.

APPENDIX 2

EUnetHTA Rapid REA UPDATE

“Renal denervation systems for treatment-resistant hypertension”, EUnetHTA WP5 Strand B, 2nd pilot rapid assessment using the HTA Core Model for Rapid Relative Effectiveness Assessment

The update was based on a basic systematic literature search in the following sources:

- Medline via Pubmed,
- EMBASE,
- Web of knowledge\ISI database,
- CRD database,
- Cochrane database.

The search period was set from June 2013 to December 2014.

References were included\excluded according to EUnetHTA PICO.

In terms of study design, SRs\HTAs, RCTs and CTs were selected to update the domains “clinical effectiveness” and “safety”.

From the selected published studies, studies characteristics and results were included into evidence tables (Table 1). The same was done for ongoing studies (Table 2).

The quality of the SRs was assessed using the English version of the NOCK checklist for SRs adapted from the Cochrane EPOC group appraisal list for SRs.

Quality of individual studies was assessed using the Cochrane risk of bias checklist (Table 3) and GRADE (Table 4 and 5).

Table 1. Published studies*Evidence tables for SRs/HTA*

Article	Meta-Analysis of the Effect of Renal Denervation on Blood Pressure and Pulse Pressure in Patients With Resistant Systemic Hypertension. Samir B. Pancholy, 2014	
Study type	Type of publication	Systematic review and meta-analysis
	Year	2014
	Last updated search	\
Research question/ main objective	To compare the effect of renal denervation (RD) with that of maximal medical therapy (MMT) on blood pressure (BP) and pulse pressure (PP) at 6-month follow-up in patients with resistant hypertension.	
Included for domain(s)	Clinical effectiveness \Safety	
Criteria for study design	<p><i>Which study design(s) are included in the assessment:</i></p> <p>-controlled trials or RCTs. Excluded observational studies, uncontrolled trials, and case reports. Included conference abstracts if they reported data relevant to the research question. The Cochrane Collaboration's risk for bias assessment tool was used to determine the quality of the included studies.</p>	
Population	Patients with resistant hypertension (RH), defined as uncontrolled hypertension (systolic BP > or = 160 mm Hg) despite treatment with 3 maximally dosed anti-hypertensive medications from 3 different classes that include a diuretic.	
Intervention	Renal denervation (RD)	
Comparator	Maximal medical therapy (MMT) for RH	
Outcomes	<p><i>Outcomes assessed:</i></p> <p>-systolic and diastolic BP at 6-month follow-up -pulse pressure (PP) Weighted mean differences (WMDs) in systolic BP, diastolic BP, and PP change at 6-month follow-up in the RD group were compared with those in the MMT group, pooling all included studies (RCTs and CTs).</p>	
Sources of information	Systematic search in MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature, OVID, the Cochrane Library database, the Web of Science, and Google Scholar for studies that assessed the effect of RD on systolic BP and diastolic BP. Eligible studies were pooled using a random-effects model.	

Studies included	5 studies included: 3 randomized controlled trials (Esler (Simplicity 2) 2010, Pokusholav 2012, Bhatt (Simplicity 3) 2014), 2 non-randomized controlled trials (Ewen 2014, Mahfoud 2014) met the inclusion criteria.											
Main results and conclusion	<p>Patients who underwent RD (n = 534) experienced significant reductions in systolic, diastolic BP and PP at 6-month follow-up. The MMT group (n = 266) also experienced significant reductions in systolic, diastolic BP and PP at 6-month follow-up. Significant reductions in systolic BP (WMD -19.4 mm Hg, p = 0.005), diastolic BP (WMD -6.4 mm Hg, p = 0.004), and PP (WMD -12.7 mm Hg, p = 0.009) were reported in the RD group when compared with the MMT group at 6-month follow-up. When the analysis was restricted to RCTs, RD's association with systolic BP lowering became weaker although significant, and the association with PP change disappeared compared with MMT, but the association with diastolic BP change at 6 months remained significant.</p> <p>Adverse events were rare and included few cases of pseudoaneurysms (n = 4 [0.7%]) and hematomas (8 [1.6%]) at the femoral sites. The most common adverse event was intra procedural bradycardia (n = 19)</p> <p>In conclusion, this meta-analysis shows that RD is superior to MMT in lowering BP, but heterogeneity among study populations in this pooled sample is high, and further data are needed to better compare these treatment strategies.</p>											
Quality assessment												
Checklist item	1	2	3	4	5	6	7	8	9	10	11	Overall quality*
Yes (Y)/ Unclear (U)/ No (N)	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	HIGH

* **High quality:** All or most criteria from the checklist are met. It is very unlikely that the study conclusions are affected.

Medium quality: Some criteria from the checklist are not met. It is unlikely that the study conclusions are affected.

Low quality: Few or no criteria in the checklist are met. It is likely that the study conclusions may be affected.

Article	Renal Denervation for Resistant Hypertension. Montreal (Canada): Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC); Nicolau, I., Dendukuri, N. 2013 Aug 30 Report no. 72.											
Study type	Type of publication	HTA										
	Country, year	Canada, 2013										
	Last updated search	April, 2013										
Research question/ main objective	To summarize the literature on efficacy, effectiveness and safety of renal denervation for treatment of resistant hypertension, and to estimate the budget impact of this technology from the perspective of the MUHC.											
Included for domain(s)	Clinical effectiveness \Safety											
Criteria for study design	<i>Which study design(s) are included in the assessment:</i> Systematic reviews and HTAs.											
Population	Patients with resistant hypertension											
Intervention	Renal denervation											
Comparator	\											
Outcomes	<i>Outcomes assessed:</i> outcomes of efficacy, effectiveness, safety and budget impact.											
Sources of information	EMBASE (Ovid), MEDLINE (PubMed) and the Cochrane Library for systematic reviews; the CRD database and websites of CADTH, INESSS, NICE and INAHTA for HTA reports.											
Studies included	1 systematic review (Gosain et al. (2013)), and 4 HTAs of other agencies; they also reviewed 1 RCT (Symplicity HTN-2), 1 cohort study (Symplicity HTN-1) cited by previous HTAs.											
Main results and conclusion	The available evidence consistently demonstrates that in patients with resistant hypertension, renal denervation is followed by a lowering of blood pressure for periods of at least 6 months and possibly up to 2 years. Longer term results are not yet available. A few manageable complications are reported, but the number of observations is still too small to be able to evaluate the frequency and severity of complications. There is a need for further research to verify the expected benefits of this procedure, to establish that they are long-lasting, and to better estimate the rate and severity of complications. The recommendation from this agency is that this technology receive temporary and conditional approval.											
Quality assessment												
Checklist item	1	2	3	4	5	6	7	8	9	10	11	Quality*

Yes (Y)/ Unclear (U)/ No (N)	Y	N	Y	Y	U	N	U	N	N	N	N\A**	MEDIUM
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** No combined results performed, thus not applicable

* **High quality:** All or most criteria from the checklist are met. It is very unlikely that the study conclusions are affected.

Medium quality: Some criteria from the checklist are not met. It is unlikely that the study conclusions are affected.

Low quality: Few or no criteria in the checklist are met. It is likely that the study conclusions may be affected.

Evidence tables for controlled trials

Article	A Controlled Trial of Renal Denervation for Resistant Hypertension. Deepak L. Bhatt, 2014 (SYMPPLICITY HTN-3 NCT01418261).		
Study type\ design	Prospective, single-blind, randomized (2:1), sham-controlled trial.		
Study objective	To evaluate the safety and effectiveness of catheter-based bilateral renal denervation for the treatment of uncontrolled hypertension despite compliance with at least 3 anti-hypertensive medications of different classes (at least 1 of which is a diuretic) at maximal tolerable doses. Designed to overcome methodological limits of previous studies (including small sample sizes, limited assessment of ambulatory blood pressure, lack of blinding, and lack of a sham procedure as a control...).		
Included for domain(s)	Clinical effectiveness \Safety		
Study inclusion/exclusion criteria*	<p>-Age ≥ 18 and ≤ 80 years at time of randomization; -stable medication regimen including full tolerated doses of 3 or more antihypertensive medications of different classes, including a diuretic (with no changes for a minimum of 2 weeks prior to screening) and no expected changes for at least 6 months; -office SBP ≥ 160 mm Hg based on an average of 3 blood pressure readings measured at both an initial and a confirmatory screening visit; -ABPM 24 hour average SBP > 135 mm Hg; -documented adherence to medications.</p> <p>Clinical exclusion criteria were known secondary causes of hypertension and more than one hospitalization for a hypertensive emergency in the previous year. Anatomical exclusion criteria were renal-artery stenosis of more than 50%, renal-artery aneurysm, prior renal-artery intervention, multiple renal arteries, a renal artery of less than 4 mm in diameter, or a treatable segment of less than 20 mm in length.</p>		
No. patients	535 from 88 sites in the United States (364 intervention group and 171 control group).		
Population	<u>Baseline characteristics</u>	<u>Intervention</u>	<u>Control</u>
	Age	57.9 \pm 10.4	56.2 \pm 11.2
	Male sex – no. (%)	215 (59.1)	110 (64.3)
	Baseline BP	\	\
	eGFR	\	\
	n hypertensive drugs	5.1 \pm 1.4	5.2 \pm 1.4
Intervention	Renal artery denervation +antihypertension medication		
Comparator	Sham treatment (renal angiography) + antihypertension medication		
Type of catheter	Symplicity		
Cointervention description	\		
Follow-up	6 months		

Outcomes	<p>Clinical effectiveness</p> <p>Primary outcome Mean change in office systolic blood pressure from baseline to 6 months in the denervation group, as compared with the mean change in the sham control group, with a superiority margin of 5 mm Hg.</p> <p>Secondary outcome change in mean 24-hour ambulatory systolic blood pressure at 6 months</p>	<p>Safety</p> <p>The primary safety end point was a composite of major adverse events, defined as death from any cause, end-stage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, or hypertensive crisis within 30 days or new renal-artery stenosis of more than 70% within 6 months. The objective performance criterion for the primary safety end point was a rate of major adverse events of 9.8%, which was derived from historical data.</p>
Results	<p>Primary outcome</p> <p><u>Between group difference:</u> change in office blood pressure from baseline at 6 months of -14.13 ± 23.93 mm Hg in the denervation group and -11.74 ± 25.94 mm Hg in the sham-procedure group, for a difference of -2.39 mm Hg (95% confidence interval [CI], -6.89 to 2.12; $P = 0.26$ with a superiority margin of 5 mm Hg).</p> <p>Secondary outcome</p> <p><u>Between group difference:</u> change in ambulatory blood pressure from baseline at 6 months of -6.75 ± 15.11 mm Hg in the denervation group and -4.79 ± 17.25 mm Hg in the sham-procedure group, for a difference of -1.96 mm Hg (95% CI, -4.97 to 1.06); $P = 0.98$ with a superiority margin of 2 mm Hg).</p>	<p>-Major adverse events: RDN 5/361 (1.4%) and the control group 1/171 (0.6%), for a difference of 0.8 percentage points (-0.9 to 2.5; $P = 0.67$). The rate in the renal-denervation group was 1.4%, therefore the performance criterion was met with a P value of <0.001.</p> <p>-There were no significant differences in safety between the two groups.</p>
Conclusion	<p>This trial doesn't show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control.</p>	

*Inclusion and exclusion criteria defined by the study protocol Catheter-Based Renal Denervation for Resistant Hypertension: Rationale and Design of the SYMPPLICITY HTN-3 Trial.

David E. Kandzari, 2012

Inclusion criteria

- Age ≥ 18 and ≤ 80 years at time of randomization
- Stable medication regimen including full tolerated doses of 3 or more antihypertensive medications of different classes, including a diuretic (with no changes for a minimum of 2 weeks prior to screening) and no expected changes for at least 6 months
- Office SBP ≥ 160 mm Hg based on an average of 3 blood pressure readings measured at both an initial and a confirmatory screening visit
- Written informed consent

Exclusion criteria

- Renal artery anatomy ineligible for treatment including:
 - Main renal arteries with < 4 mm diameter or with < 20 mm treatable length
 - Multiple renal arteries where the main renal artery is estimated to supply $< 75\%$ of the kidney
- Renal artery stenosis ($> 50\%$) or renal artery aneurysm in either renal artery
- History of prior renal artery intervention including balloon angioplasty or stenting
- eGFR of < 45 mL/min/1.73 m²
- > 1 in-patient hospitalization for a hypertensive crisis within the past year
- ABPM 24 hour average SBP < 135 mm Hg
- ≥ 1 episode(s) of orthostatic hypotension (reduction of SBP of ≥ 20 mm Hg or DBP of ≥ 10 mm Hg within 3 minutes of standing) coupled with symptoms within the past year or during the screening process
- Pregnant, nursing, or planning to be pregnant
- Chronic oxygen support or mechanical ventilation (eg, tracheostomy) required other than nocturnal respiratory support for sleep apnea
- History of or currently have any of the following medical conditions:
 - Primary pulmonary hypertension
 - Type 1 diabetes mellitus
 - Severe cardiac valve stenosis for which a significant reduction of blood pressure is contraindicated
 - Myocardial infarction, unstable angina pectoris, syncope, or a cerebrovascular accident within 6 months of the screening period
 - History of pheochromocytoma, Cushing's disease, coarctation of the aorta, hyperthyroidism, or hyperparathyroidism
- Any condition that would prohibit or interfere with ability to obtain an accurate blood pressure measurement using the protocol-specified automatic blood pressure monitor (eg, arm diameter too large for the cuff, arrhythmia that interferes with automatic monitor's pulse sensing and prohibits an accurate measurement)
- Any serious medical condition that may adversely affect the safety of the participant or the study (eg, patients with clinically significant peripheral vascular disease, abdominal aortic aneurysm, bleeding disorders such as thrombocytopenia, hemophilia, or significant anemia)
- Scheduled or planned surgery or cardiovascular intervention in the next 6 months
- Any known, unresolved history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or would be unlikely or unable to comply with study follow-up requirements
- Currently enrolled in another investigational drug or device trial

Abbreviations: ABPM, ambulatory blood pressure monitoring; DPB, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

Article	Adjusted Drug Treatment Is Superior to Renal Sympathetic Denervation in Patients With True Treatment-Resistant Hypertension. Fadl Elmula M., 2014 (NCT01673516)		
Study type\ design	Controlled, randomized (1:1) prospective study		
Study objective	To investigate for the first time the blood pressure (BP)–lowering effect of renal sympathetic denervation (RDN) versus clinically adjusted drug treatment in true treatment-resistant hypertension (TRH) after excluding patients with confounding poor drug adherence		
Included for domain(s)	Clinical effectiveness \Safety		
Study inclusion/ exclusion criteria	<p>-Patients with treatment-resistant hypertension were enrolled. TRH was defined as uncontrolled hypertension (office systolic BP [SBP] >140 mm Hg), despite regular intake of maximally tolerated doses of ≥ 3 antihypertensive drugs including a diuretic;</p> <p>-in addition, patients had to qualify by having mean ambulatory daytime SBP >135 mm Hg immediately after <u>investigator witnessed intake</u> of their antihypertensive morning drugs;</p> <p>-patients could be 18 to 80 years of age with normal renal arteries at computed tomography or MRI examination within 2 years before participation.</p> <p><u>Exclusion</u>: Patients with secondary and spurious hypertension, some patients with high serum aldosterone levels (primary hyperaldosteronism without tumor or with high aldosterone/renin activity ratio) who responded to treatment with spironolactone, Patients with estimated glomerular filtration rate <45 mL/min per 1.73 m² (MDRD formula), urine albumin/creatinine ratio >50 mg/mmol or type 1 diabetes mellitus could not be included</p>		
No. patients	19 patients with true TRH (Norway) (Drug-adjusted group (n=10) and RDN group (n=9))		
Population	<u>Baseline characteristics</u>	<u>Intervention (RDN group)</u>	<u>Control (drug-adjusted group)</u>
	Age	57 (10.9)	62.7 (5.1)
	Female sex – no. (%)	22% (2)	0% (0)
	Baseline BP (SBP/DBP) (mm Hg)	156±13/91±15	160±14/88±13
	eGFR <60 mL/min per 1.73 m ²	11% (1)	0% (0)
	n hypertensive drugs	5.1 (1.6)	5.0 (1.2)
Intervention	<u>Renal denervation</u> : antihypertensive medication was aimed at being maintained unchanged in the RDN group.		
Comparator	<u>Clinically adjusted drug treatment</u> : antihypertensive medication adjusted at baseline, 1 month, and at 3 months.		
Type of catheter	Symplicity		
Co-intervention description	\		
Follow-up	3 and 6 months (office BP measurements at 1, 3, and 6 months and ambulatory BP measurements at 3 and 6 months after the procedure§).		
Outcomes	Clinical effectiveness Change in blood pressure (BP) from randomization to 6 months	Safety (outcomes not pre-specified) Adverse events and renal function	

<p>Results</p>	<p>Clinical effectiveness <u>Drug-adjusted group</u> at 3 months: office SBP and diastolic BP changed from 160±14/88±13 mm Hg at baseline to 140±18/81±10 mm Hg ($P=0.01$ and $P=0.18$ for SBP and diastolic BP, respectively); at 6 months from 160±14/88±13 mm Hg at baseline to 132±10/77±8 mm Hg ($P<0.0005$ and $P=0.02$ for SBP and diastolic BP, respectively).</p> <p><u>RDN group</u> at 3 months: office SBP and diastolic BP changed from 156±13/91±15 mm Hg at baseline to 149±9/89±8 mm Hg ($P=0.10$ and $P=0.12$ for SBP and diastolic BP, respectively); at 6 months: from 156±13/91±15 mm Hg at baseline to 148±7/89±8 mm Hg ($P=0.42$ and $P=0.48$ for SBP and diastolic BP, respectively).</p> <p>Comparing the 2 groups, office SBP and diastolic BP were significantly lower in the drug-adjusted group at 6 months ($P=0.002$ and $P=0.004$, respectively).</p> <p>Ambulatory BPs changed in parallel to office BPs.</p>	<p>Safety</p> <p><u>Drug-adjusted group</u> 2 patients experience sexual dysfunction after increasing the dosage of spironolactone.</p> <p><u>RDN group:</u> 1 patient had a myocardial infarction 5 months after the procedure; 4 patients had mild- to-moderate hematomas at the femoral access site; 1 patient had bradycardia.</p> <p>4 patients in the drug-adjusted group and 1 patient in the RDN group had symptomatic hypotension.</p> <p>Any patient had detectable change in renal function</p>
<p>Conclusion</p>	<p>BP control through 6 months was superior by drug adjustment compared with renal denervation in patients with true TRH.</p>	

Article	Sustained Sympathetic and Blood Pressure Reduction 1 Year After Renal Denervation in Patients With Resistant Hypertension. Dagmara Hering, 2014		
Study type\ design	Controlled study		
Study objective	To assess whether the continued BP reduction associated with RDN is accompanied by long-term decrease of sympathetic outflow to the periphery in patients with resistant hypertension (RH).		
Included for domain(s)	Clinical effectiveness \Safety		
Study inclusion/ exclusion criteria	Patients with established RH were enrolled (as extensions to the Symplicity HTN-2 protocols NCT00888433). Hypertension was diagnosed based on the 2007 European Society of Hypertension and European Society of Cardiology guidelines for the management of arterial hypertension and secondary forms of hypertension were ruled out. RH was defined according to the current statement of the American Heart Association.		
No. patients	35 patients enrolled. 7 control subjects (taken from the initial control arm of the Symplicity (HTN)-2 trial and included in this analysis as a non treated control group). These 7 patients then crossed over to RDN treatment, and their data were included in the entire cohort of 35 patients who were followed-up at 3, 6, and 12 months after the procedure.		
Population	<u>Baseline characteristics</u> Age sex man/women Baseline BP (office SBP/DBP) (mmHg) eGFR, mL/min per 1.73 m ² n hypertensive drugs	<u>Intervention</u> 61±11 22/13 166±22/88±19 77.7±11.6 4.8±2.1	<u>Control</u> / / 178±11/ 94±13 / /
Intervention	Renal denervation (RDN) + antihypertensive medication		
Comparator	Only antihypertensive medication		
Type of catheter	Symplicity		
Co-intervention description	Treating physicians and patients were instructed not to change medications except when medically required.		
Follow-up	3, 6, and 12 months after RDN (assessment at baseline and 6 months in the controls)		
Outcomes	Clinical effectiveness -Reduction of office BP from baseline to 3, 6 and 12 months -Reduction in muscle sympathetic nerve activity (MSNA) after RDN	Safety (outcomes not pre-specified) -Intra- or periprocedural complications -Kidney function	
Results	<u>Mean office systolic / diastolic BP</u> significantly decreased from baseline by -12.6±18.3/-6.5±9.2, -16.1±25.6/-8.6±12.9, and -21.2±29.1/-11.1±12.9 mm Hg ($P<0.001$ for both systolic BP and diastolic BP) with	<u>RDN group:</u> -There were no intra- or periprocedural complications. No short-term (at 3-month follow-up) and long-term (≤12 months) adverse events related to	

	<p>RDN at 3-, 6-, and 12-month follow-up, respectively. <u>MSNA</u> was reduced by -8 ± 12, -6 ± 12, and -6 ± 11 bursts/min ($P<0.01$) at 3-, 6-, and 12-month follow-up.</p> <p>No significant changes in office and 24-hour BP, heart rate, and MSNA from baseline to 6-month follow-up were observed <u>in 7 patients who served as a control group.</u></p>	<p>the procedure were noted in any of the treated patients.</p> <p>-No significant alterations in kidney function as assessed by estimated glomerular filtration rate based on serum creatinine from baseline to 3-month, 6-month and 12-month follow-up ($P=0.38$) were observed. No disturbances in plasma sodium from baseline to 3-month, 6-month and 12-month follow-up ($P=0.10$) and plasma potassium from baseline to 3-month, 6-month and 12-month follow-up ($P=0.33$) were noted after the procedure.</p>
Conclusion	<p>These observations are compatible with the hypothesis of a substantial contribution of afferent renal nerve signaling to increased BP in resistant hypertension and argue against a relevant re innervation at 1 year after procedure</p>	

Article	Effects of Renal Sympathetic Denervation on Exercise Blood Pressure, Heart Rate, and Capacity in Patients With Resistant Hypertension. Ewen, 2014		
Study type\ design	Prospective controlled study		
Study objective	To investigate the effect of RDN on heart rate (HR) and blood pressure (BP) at rest, during exercise, and at recovery in patients with resistant hypertension by cycle exercise testing after a follow-up period of 6 and 12 months.		
Included for domain(s)	Clinical effectiveness		
Study inclusion/ exclusion criteria	Patients aged ≥ 18 years with resistant hypertension according to the international European Society of Hypertension guidelines (office SBP $>140/90$ mm Hg despite the use of ≥ 3 antihypertensive agents of different classes, including a diuretic at the maximum or highest tolerated dose). The inclusion and exclusion criteria were otherwise similar to the Symplicity HTN-2 trial (NCT01888315). Only patients with stable antihypertensive drug regimen were included in the study, and patients with known secondary causes of hypertension were excluded.		
No. patients	60 patients (intervention group=50, control group=10)		
Population	<u>Baseline characteristics</u> -Age -sex-men -baseline BP (office SBP\DBP) (mmHg) -eGFR -n hypertensive drugs	<u>Intervention</u> 64.7 \pm 1.0 39 (78%) 164 \pm 3\91 \pm 2 \ 5.1 \pm 0.3	<u>Control</u> 68.4 \pm 1.2 8 (80%) 155 \pm 4\87 \pm 2 \ 4.0 \pm 0.4
Intervention	Bilateral RDN + antihypertension medication		
Comparator	Not treated with RDN (only antihypertension medication)		
Type of catheter	Symplicity		
Co intervention description	Patients and physicians were instructed not to change antihypertensive medication during the study period, except when medically required.		
Follow-up	6 and 12 months		
Outcomes	-Reduction of office BP from baseline to 6 months -Change in BP and HR after exercise (Exercise Stress Test) -Mean exercise time and mean workload	\	
Results	-At 6-month FU, office BP was reduced by 26/7 mm Hg from 164 \pm 3/91 \pm 2 to 138 \pm 3/84 \pm 2 mm Hg in the RDN group ($P<0.001/P<0.001$), whereas there was no significant change (-2/0 mm Hg from 155 \pm 4/87 \pm 2 to 153 \pm 5/87 \pm 1 mm Hg; $P=0.750/P=0.611$) in the control	\	

	<p>group.</p> <p><u>After RDN at rest:</u> -exercise BP reduced from 158±3/90±2 to 141±3/84±4 mm Hg ($P<0.001$ for systolic blood pressure/$P=0.007$ for diastolic blood pressure) after 6 months - BP reduced from 158±3/90±2 to 139±3/83±4 mm Hg ($P<0.001/P=0.022$) after 12 months. -HR reduced from 71±3 bpm to 66±2 ($P<0.001$) after 6 months and to 69±3 ($P=0.092$) after 12 months.</p> <p><u>After RDN during exercise:</u> BP tended to be lower at all stages of exercise at 6- and 12-month follow-up.</p> <p><u>After RDN at recovery after 1 minute:</u> -BP decreased from 201±4/95±2 to 177±4/88±2 ($P<0.001/P=0.066$) after 6 months -BP reduced from 201±4/95±2 to 188±6/86±2 mm Hg ($P=0.059/P=0.01$) after 12 months; -HR at recovery after 1 minute reduced from 96±5 bpm to 89±3 bpm ($P=0.008$) after 6 months and to 93±4 bpm ($P=0.032$) after 12 months.</p> <p><u>No changes were observed in the control group</u></p> <p>-Mean exercise time and mean workload in the RDN group increased significantly by 1.41±0.04 minutes ($P<0.001$) and 7±1 W ($P<0.001$) at 6-month FU and by 2.01±0.06 minutes ($P=0.008$) and 8±2 W ($P=0.007$) at 12-month FU.</p> <p><u>Control: any significant change ($P=0.555$ and $P=0.486$, respectively)</u></p>	
<p>Conclusion</p>	<p>In conclusion, this study shows that RDN reduced BP and HR at rest, during exercise, and at recovery, and improved exercise capacity measured by workload and exercise time.</p>	

Article	Renal nerve ablation reduces augmentation index in patients with resistant hypertension. Hering, 2013		
Study type\ design	Prospective controlled study		
Study objective	To examine whether sympathetic nerve ablation affects peripheral arterial stiffness assessed as augmentation index in high-risk patients with resistant hypertension, in order to understand if alterations of arterial stiffness may contribute to BP control (assessing the effects of RDN on augmentation index).		
Included for domain(s)	Clinical effectiveness \Safety		
Study inclusion/ exclusion criteria	Hypertension was diagnosed on the basis of the current European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines for the management of arterial hypertension. Patients had previously been screened for secondary forms of hypertension as listed in the current guidelines and were excluded if present, with the exception of obstructive sleep apnoea. Resistant hypertension was defined according to the current statement of the American Heart Association. Only patients with true resistant hypertension, as verified by daytime SBP of more than 135mmHg, were included in this study. All patients had renal artery imaging prior to enrolment to exclude severe renal artery stenosis or other abnormalities such as fibromuscular dysplasia.		
No. patients	50 consecutive patients with resistant hypertension enrolled: 40 RDN-group and 10 controls		
Population	<u>Baseline characteristics</u> -Age -sex (men\women) -baseline BP (office SBP\DBP) (mmHg) -eGFR (ml\min\1.73m2) -n hypertensive drugs	<u>Intervention (40)</u> 60 ±11 31\9 170± 19\92±15 74.3± 17.6 4.9+ 1.9	<u>Control (10)</u> 60±6 8\2 171±14\93±8 84.4± 9.1 4.4+ 2.0
Intervention	Renal denervation (RDN) + antihypertension medication		
Comparator	Non-RDN (only antihypertension medication)		
Type of catheter	Symplicity		
Co intervention description	\		
Follow-up	3 months		
Outcomes	Clinical effectiveness -Reduction of office-seated and ambulatory blood pressure -improvement of augmentation index and MSNA	Safety -complications during\after procedure (not pre-specified) -kidney function tests were repeated at 3-month follow-up (pre-specified as safety outcome)	

Results	<p>Clinical effectiveness -RDN significantly reduced seated-office SBP (170± 19 vs 154± 25 mmHg; P<0.001) and DBP (92± 15 vs 84±16 mmHg; P<0.001) at 3-month follow-up (decrease of 16/8mmHg (SD 21/11), respectively).</p> <p>No changes in office SBP and DBP at 3-month follow-up in hypertensive controls (171± 14 versus 169 ±11; p=0.63 and 93±8 versus 92± 11; p=0.69).</p> <p>-Augmentation index was significantly reduced 3 months after the procedure in RDN patients (30.6±23.8 vs. 22.7±22.4%; P=0.002), but not in non-RDN controls (30.2±27.4 vs. 32.0±20.7%; P=0.80).</p> <p>-MSNA significantly decreased 3 months following RD, but there were no changes in MSNA in non-RDN controls.</p>	<p>Safety</p> <p><u>RDN group:</u></p> <p>-There were no intraprocedural or periprocedural complications. No short-term (at 3-month follow-up) adverse events related to the procedure were noted in any of the treated patients</p> <p>-No significant alterations in kidney function assessed by estimation of GFR based on serum creatinine (74.3 ±17.6 vs. 71.9± 18.0 ml/min per 1.73m²; P=0.31), plasma potassium (4.0 ±0.4 vs. 4.1±0.5 mmol/l; P=0.93) and sodium (139.2±2.4 vs. 139.0± 2.1 mmol/l; P=0.50) levels after RDN.</p>
Conclusion	<p>In conclusion, RDN results in a substantial and rapid reduction in augmentation index, which appears to be independent of BP and MSNA changes. These findings indicate that RDN may exert a beneficial effect on arterial stiffness in patients with resistant hypertension.</p>	

Article	Effect of renal denervation on left ventricular mass and function in patients with resistant hypertension: data from a multi-centre cardiovascular magnetic resonance imaging trial. Mahfoud, 2014		
Study type\ design	Controlled trial		
Study objective	The present multi-centre study aimed to investigate the effect of RDN on anatomic and functional myocardial parameters, assessed by cardiac magnetic resonance (CMR), in patients with resistant hypertension compared to a control group of medical treated patients		
Included for domain(s)	Clinical effectiveness		
Study inclusion/ exclusion criteria	Patients with resistant hypertension. Enrolled subjects ≥ 18 years with an office systolic blood pressure (SBP) above goal (≥ 140 mm Hg) or mean ambulatory 24-h SBP > 135 mm Hg despite the use of ≥ 3 antihypertensive agents of different classes, including a diuretic at maximum or highest tolerated doses. Patients with pseudo-resistant hypertension defined as mean ambulatory 24-h SBP < 130 mm Hg were excluded. Patients with GFR < 45 mL/min/1.73 m ² and patients on haemodialysis were excluded. Patients with general contraindications for CMR were excluded. Only patients with stable antihypertensive drug regimen were included and patients with known, treatable secondary causes of hypertension were excluded.		
No. patients	72 patients with resistant hypertension were enrolled in the study. 55 subjects were treated with RDN and 17 subjects served as controls (medical treatment only).		
Population	<u>Baseline characteristics</u> -Age -sex: Male (%) -baseline BP (office SBP\DBP) (mmHg) -eGFR -n hypertensive drugs	<u>Intervention (55)</u> 65 \pm 10 39 (71%) 170.0 \pm 21.4 \ 89.9 \pm 14.8 \ 4.6 \pm 1.6	<u>Control (17)</u> 70 \pm 9 10 (59%) 157.4 \pm 15.3 \ 83.8 \pm 10.9 \ 4.5 \pm 1.2
Intervention	Renal denervation (RDN) + antihypertensive medication		
Comparator	Medical treatment only		
Type of catheter	Symplicity		
Co-intervention description	\		
Follow-up	6 months		
Outcomes	Clinical effectiveness -End systolic\ end diastolic volume (LVESVI and LVEDVI assessed) -LV mass, assessed by cardiac magnetic resonance (CMR). Left	\	

	<p>ventricular mass was then normalized indexing to body surface area and height (g/m^{1.7})</p> <p>-Ejection fraction</p> <p>-SBP and DBP reported</p>	
Results	<p>Clinical effectiveness -No significant changes between baseline and 6 months were evident for LVESV, however for LVEDV in the RDN group (LVEDV: 177±54 mL vs. 176±53; P=0.246 and LVESV: 81±40 mL vs. 77±35 mL; P=0.038). No significant changes between baseline and 6 months were evident for LVESV and LVEDV in the controls.</p> <p>-Left ventricular mass indexed to height^{1.7} significantly decreased by 7.1% 6 months after RDN (from 46.3±13.6 to 43.0±12.6 g/m^{1.7}, P < 0.001). In the control group, LV mass remained unchanged (41.9±10.8 vs. 42.0±9.7 g/m^{1.7}, P =0.653)</p> <p>-Ejection fraction increased significantly after RDN(55.7±11.1 vs. 57.6±9.3%, P = 0.048) and remained unchanged in the control group (55.9±8.2 vs. 55.5±8.4%, P = 0.723).</p> <p>-Office SBP / DBP decreased significantly from 170/90 ±21/15 mm Hg at baseline to 148/82±19/14 mm Hg (P < 0.001) 6 months after RDN. SBP/DBP in the control group did change during follow-up (156/84±17/11 vs. 145/77±23/15 mm Hg; P=0.044 for SBP and P=0.034 for DBP).</p>	\
Conclusion	Renal denervation reduced BP and significantly improved LVH and myocardial function, as diagnosed by CMR, in patients with resistant hypertension.	

Table 2. Ongoing studies

ID	Study name	Health condition (selected criteria) Target sample size	Intervention	Control	Primary Outcomes
NCT02295683	Renal Sympathetic Denervation by Iberis System in Patients With Uncontrolled Hypertension - Iberis-HTN Registry	Resistant Hypertension. N=30	Device: Renal Denervation	Patient Registry	Blood Pressure (BP) Measurements [Time Frame: Up to 5 year FU]
NCT02164435	Effects of Renal Sympathetic Denervation on the Cardiac and Renal Functions in Patients With Drug-resistant Hypertension Through MRI Evaluation	Uncontrolled Hypertension N=20	Procedure: Renal Denervation (EnligHTN™) Renal artery ablation with the EnligHTN™ Renal Denervation System	Endpoint Classification: safety /Efficacy Study, Intervention Model: Single Group Assignment, Masking: Open Label, Primary Purpose: Treatment	Cardiac Function (evaluated by MRI) [Time Frame: baseline 6 months and 24 months]
NCT02155790	Safety and Performance Study of Renal Denervation by Neurolysis	Hypertension N= 20	Device: Injection of a neurolytic agent for denervation of the renal sympathetic nerves Device: The Ablative Solutions Peregrine Infusion Catheter	Endpoint Classification: Safety/Efficacy Study, Intervention Model: Single Group Assignment, Masking: Open Label, Primary Purpose: Treatment	- Cerebrovascular accident; - Grade 3 or 4 hemorrhage; -Myocardial infarction; -Reduction in the systolic blood pressure of at least 10% [3 months]; -Sudden cardiac death; -Vessel dissection or perforation
NCT02115230	Renal Denervation in Patients With Heart Failure With Normal LV Ejection Fraction	Heart Failure, Diastolic Hypertension N=40	Procedure: Renal denervation + medical therapy	Study described as allocation Randomized. Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Open Label, Primary Purpose: Treatment	Efficacy: Change from baseline E/E' on echocardiography at 12 months; Safety: Composite of death, myocardial infarction, cerebrovascular event, need of intervention on renal arteries and renal function impairment (decrease in estimated GFR > 30% from baseline) [Time Frame: 12 months]
NCT02057224	Metabolic and Cardiovascular Effects of Renal Denervation	Hypertension Insulin Resistance N=15	Renal denervation using Medtronic Symplicity System (mono-electrode)	Endpoint Classification: Bio-availability Study, Intervention Model: Single Group Assignment, Masking: Open Label, Primary Purpose: Treatment	Adipose tissue function [Time Frame: 6 months after renal denervation]
NTR4384	Feasibility of electrical mapping and stimulation of renal arteries in patients undergoing renal	Hypertension N= 60	Renal denervation Pulmonary vein isolation	No Randomized; Masking: None; Control: Not applicable; Group: Parallel; Type: 2 or more arms,	Arterial blood pressure response to renal nerve stimulation prior to renal denervation and absence of blood pressure rise in

	denervation			non-randomized	response to pacing in the renal artery after renal denervation
NCT02039492	Sympathetic Renal Denervation Versus Increment of Pharmacological Treatment in Resistant Arterial Hypertension	Resistant Arterial Hypertension N=50	Drug: Treatment with aldactone Procedure: Sympathetic Renal Denervation	Study described as allocation: randomized. Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Open Label, Primary Purpose: Treatment	Changes in ambulatory 24h- systolic blood pressure [Time Frame: From baseline (Visit 0) to Final Examination (6 months).]
NCT02016573	Renal Denervation for Uncontrolled Hypertension	Hypertension N=100	Device: Renal Denervation	Study described as allocation: Randomized. Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Open Label, Primary Purpose: Treatment	Blood pressure control [Time Frame: 6 months post procedure]
NCT02006758	Observational Study of the EnligHTN Renal Denervation System in Patients With Uncontrolled Hypertension	Uncontrolled Hypertension. N=500	Device: EnligHTN™ Renal Denervation System	Observational Model: Case-Only, Time Perspective: Prospective	Mean reduction in office Systolic BP [Time Frame: 6 months]
NCT01990911	Renal Sympathetic Denervation Prevents Atrial Fibrillation in Patients With Hypertensive Heart Disease: a Pilot Study RDPAF	Atrial Fibrillation Autonomic Imbalance Hypertension Hypertensive Heart Disease N=100	Device: Renal denervation Drug: Medical therapy	Study described as allocation Randomized. Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Single Blind (Subject), Primary Purpose: Prevention	Atrial fibrillation [Time Frame: 3 years]
JPRN-UMIN000012020	Study of Renal Sympathetic Denervation with Radiofrequency Ablation Catheter for Resitant Essential Hypertension	Drug-Resistant Essential Hypertension N=6	Renal sympathetic denervation with radiofrequency ablation catheter	Single arm Non-randomized	- Safety during perioperative period and chronic phase after the operation (evaluated with eGFR and imaging study) - Onset or progression of cardiovascular disease

Table 3. Risk of bias tables for the “clinical effectiveness” domain

Quality of the controlled studies was assessed using the Cochrane risk of bias check-list for RCTs.

Entry (Fadl Elmula, 2014) RCT	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	“Patients were randomized using a permuted block randomization list”
Allocation concealment (selection bias)	Low risk of bias	“Patients were randomized (using a permuted block randomization list) through a telephone call to a hospital employee who was not involved in the study, who was uninformed about the nature of the study, and who opened a sealed envelope arranged in a fixed order and documented in writing the outcome of the randomization.”
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Blinding not performed or not reported, unclear as to how this could influence compliance with pharmacological medication and have effect on BP.
Blinding of outcome assessment (detection bias)	Unclear risk of bias	“All patients and all BP measurements during follow-up were handled by the same experienced physicians (F.M.F., A.C.L.) using the same calibrated and validated devices.”
Incomplete outcome data assessed (attrition bias)	Low risk of bias	No incomplete data
Selective reporting (reporting bias)	Unclear risk of bias	As pre-specified, office and ambulatory BP were assessed and reported. Heart rate and safety outcomes not pre-specified, but reported.
Other biases	Unclear risk of bias	The study was funded by Oslo University Hospital, University of Oslo, and the South-Eastern Norway Health Region. F.E.M. Fadl Elmula has received lecture honoraria from Medtronic and Hemo Sapiens. P. Hoffmann has received travel grant from Medtronic. A.C. Larstorp has received lecture honoraria from Hemo Sapiens and Merck Sharpe & Dome. E. Fossum has received lecture honoraria from St. Jude and travel grant from Medtronic. M. Brekke has received lecture honoraria from St. Jude and consulting honoraria from Boston Scientific. S.E. Kjeldsen has received lecture honoraria from AstraZeneca, Bayer, Medtronic, Merck Sharpe & Dome, and Takeda; honoraria for consulting from Bayer, Medtronic, Serodius, and Takeda; and research support from AstraZeneca, Hemo Sapiens, and Pronova. A. Hoiegggen has received lecture honoraria from Amgen, AstraZeneca, Novartis, and St. Jude. The other authors report no conflicts.

Entry (Hering, 2014) CT	Judgement	Support for judgement
Random sequence generation (selection bias)	High risk of bias	Randomization not performed or reported. Unclear if Simplicity HTN-2 protocol was followed.
Allocation concealment (selection bias)	Unclear risk of bias	It is unclear how patients were allocated. Unclear if Simplicity HTN-2 protocol was followed. Study provides 35 patients enrolled as extensions to the Symplicity protocols. 7 control subjects (taken from the initial control arm of the Symplicity (HTN)-2 trial and included in this analysis as a non treated control group), then crossed over to RDN treatment, and their data were included in the entire cohort of 35 patients who were followed-up at 3, 6, and 12

		months after the procedure. "Thirty-five patients with established RH were enrolled as extensions to the Symplicity protocols" and 7 control"
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Blinding not performed or not reported, unclear how this could influence compliance with pharmacological medication and have effect on BP. Unclear if Symplicity HTN-2 protocol was followed.
Blinding of outcome assessment (detection bias)	Low risk of bias	Analysers blinded to treatment. "Changes in MSNA recording were performed and analyzed by an experienced investigator without the knowledge of the patient identity and treatment status"
Incomplete outcome data assessed (attrition bias)	High risk of bias	Some data missing for ABPM. "At 3-month follow-up, ABPM recordings were only available from 24 patients because the remaining 11 patients were participants of the Symplicity HTN-2 trial, the protocol of which required ABPM to be performed at 6-month but not at 3-month follow-up."
Selective reporting (reporting bias)	Low risk of bias	None detected
Other biases	Low risk of bias	This study was funded, in part, by grants from the National Health and Medical Research Council of Australia and the Victorian Government's Operational Infrastructure Support Program and by Medtronic. The funding organizations played no role in the design and conduct of the study, collection, management, analysis or interpretation of the data, or preparation, review, or approval of the article.

Entry (Bhatt, 2014) RCT	Judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk of bias	Not specified how the sequence was generated. "Patients 18 to 80 years of age with resistant hypertension were randomly assigned in a 2:1 ratio to undergo renal artery denervation or a sham procedure"
Allocation concealment (selection bias)	Low risk of bias	Randomization is accomplished at the time of the renal angiogram using an interactive voice response system. (Kandzari)
Blinding of participants and personnel (performance bias)	Low risk of bias	Participants blinded. "Patients were unaware of whether they underwent renal-artery denervation or renal angiography only (sham control)".
Blinding of outcome assessment (detection bias)	Low risk of bias	Blood-pressure assessors were also unaware of the study-group assignments.
Incomplete outcome data assessed (attrition bias)	Low risk of bias	None detected.
Selective reporting (reporting bias)	Low risk of bias	The study protocol available and all pre-specified outcomes reported.
Other biases	Unclear risk of bias	Funded by Medtronic.

Entry (Ewen, 2014) CT	Judgement	Support for judgement
Random sequence generation (selection bias)	High risk of bias	Randomization not performed or reported.
Allocation concealment (selection bias)	Unclear risk of bias	It is unclear how patients were allocated. "Fifty patients underwent bilateral RDN, and 10 patients were assigned to the control group."
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Blinding not performed or not reported, unclear as to how this could influence compliance with pharmacological medication and have effect on BP. "Patients performed bicycle exercises under the supervision of a physician blinded to the RDN status"
Blinding of outcome assessment (detection bias)	Unclear risk of bias	"BP was measured by an experienced physician using a manual sphygmomanometer."
Incomplete outcome data assessed (attrition bias)	Low risk of bias	None detected.
Selective reporting (reporting bias)	Low risk of bias	None detected.
Other biases	Unclear risk of bias	The institution has received scientific support from Medtronic/ Ardian. F. Mahfoud and M. Böhm were investigators of Symplicity HTN-1 and HTN-2 trial. F. Mahfoud, C. Ukena, and M. Böhm have received speaker honorarium and consultancy fees from Medtronic/ Ardian, St. Jude, Boston Scientific, and Cordis. C. Ukena, U. Laufs, and M. Böhm are supported by Deutsche Forschungsgemeinschaft (KFO 196). S. Ewen and F. Mahfoud are supported by Deutsche Hochdruckliga. F. Mahfoud and M. Böhm are supported by Deutsche Gesellschaft für Kardiologie. The other authors report no conflicts.

Entry (Mahfoud, 2014) CT	Judgement	Support for judgement
Random sequence generation (selection bias)	High risk of bias	"The non-randomized study design and the small sample size are limitations of this study"
Allocation concealment (selection bias)	Unclear risk of bias	Allocation is not described. Seventy-two patients with resistant hypertension were enrolled in the study. Fifty-five subjects were treated with RDN and 17 subjects served as controls (medical treatment only).
Blinding of participants and personnel (performance bias)	Low risk of bias	Blinding of patients not performed or not reported, but outcomes like LV mass and function unlikely to be affected.
Blinding of outcome assessment (detection bias)	Low risk of bias	Clinical data and CMR results were analysed blindly.
Incomplete outcome data assessed (attrition bias)	Low risk of bias	No patient was lost to follow-up during the study period of 6 months.
Selective reporting (reporting bias)	Low risk of bias	None detected.
Other biases	Unclear risk of bias	Conflict of interest: All institutions received scientific support from Medtronic/Ardian. F.M., M.P.S., M.D.E., and M.B. were investigators of Symplicity HTN-1 and HTN-2 trial. F.M., M.P.S., M.D.E., and M.B. Have received speaker honorarium and consultancy fees from Medtronic/ Ardian, St. Jude, Boston Scientific, and/or Cordis.

Entry (Hering, 2013) CT	Judgement	Support for judgement
Random sequence generation (selection bias)	High risk of bias	Randomization not performed or reported; it is only reported that it is a prospective clinical study. 40 patients underwent the procedure. Ten patients, who were eligible for the procedure but did not undergo RDN at the time, served as controls (non-RDN).
location concealment (selection bias)	Unclear risk of bias	It is unclear how patients were allocated.
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Blinding not performed or not reported: outcomes like MSNA and augmentation index unlikely to be influenced, but unclear if BP would be influenced.
Blinding of outcome assessment (detection bias)	Low risk of bias	Data analysis performed blinded . "A random code was attributed to all recordings and all data analyses (of augmentation index, AI@75 and MSNA) were performed blinded to the identity of the patient and measurement (at baseline and at 3-month follow-up) during which the recording had been performed.
Incomplete outcome data assessed (attrition bias)	High risk of bias	Some data missing for ABPM. "At 3-month follow-up, analysable ABPM data were available from 23 out of 37 patients. The remaining 14 patients were participants of the Symplicity HTN-2 trial, the protocol of which required ABPM to be performed at 6-month but not at 3-month follow-up."
Selective reporting (reporting bias)	Low risk of bias	None detected
Other biases	Unclear risk of bias	Conflicts of interest: A.S.W., H.K., F.M., M.B., M.D.E. and M.P.S. are investigators in studies sponsored by Medtronic. P.A.S. is a previous employee of Medtronic.

Risk of bias – Blood Pressure

	RISK OF BIAS*						
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data assessed (attrition bias)	Selective reporting (reporting bias)	Other biases
Fadl Elmula, 2014	+	+	?	?	+	?	?
Hering, 2014	-	?	?	+	-	+	+
Bhatt, 2014*	?	+	+	+	+	+	?
Ewen, 2014*	-	?	?	?	+	+	?
Mahfoud, 2014*	-	?	+	+	+	+	?
Pokushalov 2012**	+	+	+	+	+	-	?
Esler 2010 (HTN-2)**	+	+	?	?	+	?	?

* Studies included in the meta-analysis (Pancholy 2014)

**Studies included in the meta-analysis (Pancholy 2014), but already reported in EUnetHTA report.

Risk of bias- mortality and cardiovascular morbidity

	RISK OF BIAS*						
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data assessed (attrition bias)	Selective reporting (reporting bias)	Other biases
Mahfoud, 2014	-	?	+	+	+	+	?

Risk of bias – activities of daily living

	RISK OF BIAS*						
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data assessed (attrition bias)	Selective reporting (reporting bias)	Other biases
Ewen, 2014	-	?	?	?	+	+	?

+	high risk of bias
-	low risk of bias
?	unclear risk of bias

Table 4. GRADE- clinical effectiveness domain

GRADE profiles for “clinical effectiveness” - BP

Quality assessment							N. of patients		Effect		Quality	Importance
N. of studies	Design	Risk of bias	Inconsistency \Heterogeneity	Indirectness	Imprecision	Other considerations (publication bias)	Renal denervation	Control	Relative (95% CI)	Absolute		
Change in systolic BP (SBP) at 6 months (follow-up 6 months; measured with: office-based (mmHg); better indicated by lower values)												
5 (Pancholy, 2014)	(R)CTs	Serious risk of bias ³⁰	Serious inconsistency ³¹	Serious indirectness ³²	No serious imprecision ³³	None	534	266	-	MD 19.36 lower (-32.80 to -5.92, P =0.005)	VERY LOW	CRITICAL
1 (Fadl Elmula, 2014)	RCT	No serious risk of bias ³⁴	Only one study---no serious inconsistency	Not serious indirectness ³⁵	Very serious ³⁶	None	9	10	-	From 156±13 to 148±7 (P=0.42) VS from 160±14 to 132±10 (P<0.0005). Between group difference: SBP significantly lower in the drug-adjusted group at 6 months (P=0.002)	LOW	CRITICAL

³⁰ Mixed randomized (3) and non-randomized (2) CT (combined as in the SR). In 2 CTs unclear how allocation was performed, in 1 CT and 1 RCT blinding not performed or not reported, unclear how this could influence compliance with pharmacological medication and have effect on BP.

³¹ $P < 0.00001$ $I^2=93\%$

³² $I^2=4$ studies use one type of catheter (Simplicity), 1 CT doesn't use Simplicity, uncertain transferability; $P=2$ CT use 140 mmHg as threshold to define RH; 3 RCT use 160 mmHg (even if the meta-analysis reports that all included studies uses 160 as reference). 1 CT involves patients with resistant hypertension and atrial fibrillation and 1 CT excludes patients with general contraindications for cardiac magnetic resonance.

³³ Appropriate number of participants, total CI does not cross the null effect

³⁴ Blinding not performed or not reported, unclear how this could influence compliance with pharmacological medication and have effect on BP.

³⁵ The BP threshold for the enrolment was > 140 mmHg, $I^2=$ only 1 catheter

³⁶ Small sample size (19); only one study: unknown reproducibility.

1 (Hering, 2014)	CT	Serious risk of bias ³⁷	Only one study--no serious inconsistency	Not serious indirectness ³⁸	Very serious ³⁹	none	35	7	-	Mean office systolic BP significantly decreased from baseline by -16.1±25.6 mm Hg (P<0.001) with RDN at 6--month follow-up Control:Office SBP, mmHg from 178±11 to 174±8 p=0.38	VERY LOW	CRITICAL
Change in diastolic BP (DBP) at 6 months (follow-up 6 months; measured with: office-based (mmHg); better indicated by lower values)												
5 (Pancholy, 2014)	(R)CTs	Serious risk of bias ⁴⁰	Serious inconsistency ⁴¹	Serious indirectness ⁴²	No serious imprecision ⁴³	None	534	266	-	MD 6.38 lower (-10.73 to -2.03, P=0.004)	VERY LOW	CRITICAL
1 (Fadl Elmula, 2014)	RCT	No serious risk of bias ⁴⁴	Only one study--no serious inconsistency	No serious indirectness ⁴⁵	Very serious ⁴⁶	None	9	10	-	From 91±15 to 89±8 (P=0.48) VS from 88±13 to 77±8 (P=0.02). Between group difference: DBP	LOW	CRITICAL

³⁷ Controlled but not randomized trial, unclear how allocation was performed, unclear if blinding was performed. Some data seem to miss.

³⁸ I =only 1 catheter, P= specific selection criteria not specified, other than the definition of RH according to American Heart Association criteria.

³⁹ Small sample size (35); only one study: unknown reproducibility

⁴⁰ Mixed randomized (3) and non-randomized (2) CT (combined as in the SR). In 2 CTs unclear how allocation was performed, in 1 CT and 1 RCT blinding not performed or not reported, unclear as to how this could influence compliance with pharmacological medication and have effect on BP.

⁴¹ P=0.02; I²=67%

⁴² I= 4 studies use one type of catheter (Simplicity), 1 CT doesn't use Simplicity, uncertain transferability; P= 2 CT use 140 mmHg as threshold to define RH; 3 RCT use 160 mmHg (even if the meta-analysis reports that all included studies uses 160 as reference). 1 CT involves patients with resistant hypertension and atrial fibrillation and 1 CT excludes patients with general contraindications for cardiac magnetic resonance.

⁴³ Appropriate number of participants, total CI does not cross the null effect.

⁴⁴ Blinding not performed or not reported, unclear how this could influence compliance with pharmacological medication and have effect on BP.

⁴⁵ The BP threshold for the enrollment was > 140 mmHg, I =only 1 catheter.

⁴⁶ Small sample size (19); only one study: unknown reproducibility.

										significantly lower in the drug-adjusted group at 6 months (P=0.004).		
1 (Hering, 2014)	CT	Serious risk of bias ⁴⁷	Only one study--no serious inconsistency	No serious indirectness ⁴⁸	Very serious ⁴⁹	none	35	7	-	Mean office diastolic BP_ significantly decreased from 92±15 to 84±16 mmHg; P<0.001)at 3-month follow-up. (by - 8.6±12.9 mm Hg(P<0.001) with RDN at 6--month follow-up. Control: office DBP, mmHg from 94±13 to 92±16 p=0.26	VERY LOW	CRITICAL

GRADE profiles for “clinical effectiveness” - mortality and cardiovascular morbidity

Quality assessment							N. of patients		Effect		Quality	Importance
N. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (publication bias)	Renal denervation	Control	Relative (95% CI)	Absolute		
Outcome: LV mass post treatment (follow-up 6 months; measured with: LV mass indexed to height 1.7 (g/m1.7); better indicated by lower values)												

⁴⁷ Controlled but not randomized trial, unclear how allocation was performed, unclear if blinding was performed. Some data seem to miss

⁴⁸ I=only 1 catheter, P= specific selection criteria not specified, other than the definition of RH according to American Heart Association criteria.

⁴⁹ Small sample size (35); only one study: unknown reproducibility

1 (Mahfoud, 2014)	CT	Serious risk of bias ⁵⁰	Only one study--no serious inconsistency	Not serious indirectness ⁵¹	Very serious ⁵²	none	55	17	-	Left ventricular mass indexed to height1.7 significantly decreased by 7.1% 6 months after RDN (from 46.3±13.6 to 43.0±12.6 g/m1.7, P < 0.001). In the control group, LV mass remained unchanged (41.9±10.8 vs. 42.0±9.7 g/m1.7, P =0.653)	VERY LOW	IMPORTANT
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GRADE profiles for “clinical effectiveness” - activities of daily living

Quality assessment							N. of patients		Effect		Quality	Importance
N. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (publication bias)	Renal denervation	Control	Relative (95% CI)	Absolute		
Outcome: change in mean exercise time (follow-up 6 months; measured with: minutes; better indicated by higher values)*												
1 (Ewen, 2014)	CT	Serious ⁵³	Only one study---no	Not serious indirectness ⁵⁴	Very serious ⁵⁵	none	50	10	-	Mean exercise time in the	VERY LOW	IMPORTANT

⁵⁰ Controlled but not randomized trial, unclear how allocation was performed.

⁵¹ The BP threshold for the enrollment was > 140 mmHg and patients with general contraindications for cardiac magnetic resonance were excluded, I =only 1 catheter.

⁵² Small sample size (72); only one study: unknown reproducibility

⁵³ Controlled but not randomized trial, unclear how allocation was performed, unclear if blinding was performed.

⁵⁴ The BP threshold for the enrollment was > 140 mmHg, I =only 1 catheter.

⁵⁵ Small sample size (60); only one study: unknown reproducibility

			serious inconsistency							RDN group increased significantly by 1.41±0.04 minutes (P<0.001) at 6-month. Control: any significant change (P=0.555)		
Outcome: change in mean workload (follow-up 6 months; measured with: Watts; better indicated by higher values)*												
1 (Ewen, 2014)	CT	Serious ²⁴	Only one study---no serious inconsistency	Not serious indirectness ²⁵	Very serious ²⁶	none	50	10	-	Mean workload in the RDN group increased significantly by 7±1 W (P<0.001) at 6-month. Control: any significant change (P=0.486)	VERY LOW	IMPORTANT

*exercise capacity measured by workload and exercise time

Table 5. GRADE – Safety domain

GRADE profiles for “safety”

Quality assessment						N. of patients		Effect	Quality	Importance
N. of studies	Design	Risk of bias	Inconsistency\H eterogeneity	Indirectness	Other considerations (publication bias)	Renal denervation	Control	Absolute (I vs. C)		
Total adverse events (in % of patients)										
5 (Pancholy, 2014)	(R)CTs	Serious risk of bias ⁵⁶	No serious inconsistency ⁵⁷	Serious indirectness ⁵⁸	none	534	266	31/534 (5.8%) versus not reported	LOW	CRITICAL
1 (Fadl Elmula, 2014)	RCT	Serious risk of bias ⁵⁹	Only one study, no serious inconsistency	Not serious indirectness	none	9	10	7/9 (77.8%) versus 6/10 (60%)	MODERATE	CRITICAL
1 (Hering, 2014)	CT	Very serious risk of bias ⁶⁰	Only one study, no serious inconsistency	Not serious indirectness	none	35	7	0 versus not reported	VERY LOW	CRITICAL
1 (Hering, 2013)	CT	Very serious risk of bias ⁶¹	Only one study, no serious inconsistency	Not serious indirectness	none	40	10	0 versus not reported	VERY LOW	CRITICAL
Major adverse events (in % of patients)										

⁵⁶ Mixed randomized (3) and non-randomized (2) CT (combined as in the SR): only the 3 RCTs report safety. In 1 RCT blinding not performed or not reported, unclear how this could influence compliance with pharmacological medication and have effect on safety aspects. 1 RCT with unclear risk of reporting bias, 1 RCT with high risk of reporting bias, only 1 RCT with clearly pre-specified safety outcomes.

⁵⁷ Not reported.

⁵⁸ I= 4 studies use one type of catheter (Simplicity), 1 CT doesn't use Simplicity, uncertain transferability; P= 2 CT use 140 mmHg as threshold to define RH; 3 RCT use 160 mmHg (even if the meta-analysis reports that all included studies uses 160 as reference). 1 CT involves patients with resistant hypertension and atrial fibrillation and 1 CT excludes patients with general contraindications for cardiac magnetic resonance.

⁵⁹ Blinding not performed or not reported, unclear how this could influence compliance with pharmacological medication and have effect on safety aspects, safety outcomes are not pre-specified and defined.

⁶⁰ Controlled but not randomized trial, unclear how allocation was performed, unclear if blinding was performed, safety outcomes are not defined and pre-specified and authors only report that no adverse events related to the procedures occurred in the treated patients.

⁶¹ Controlled but not randomized trial, unclear how allocation was performed, unclear if blinding was performed, safety outcomes are not all defined and pre-specified and authors only report that there were no intraprocedural or periprocedural complications.

5 (Pancholy, 2014)	(R)CTs	Serious risk of bias ¹	No serious inconsistency ²	Serious indirectness ³	none	534	266	Not specified	LOW	CRITICAL
1 (Fadl Elmula, 2014)	RCT	Serious risk of bias ⁴	Only one study, no serious inconsistency	Not serious indirectness	none	9	10	1/9 (11.1%) versus 2/10 (20%)	MODERATE	CRITICAL
1 (Hering, 2014)	CT	Serious risk of bias ⁵	Only one study, no serious inconsistency	Not serious indirectness	none	35	7	0 versus not reported	VERY LOW	CRITICAL
1 (Hering, 2013)	CT	Serious risk of bias ⁶	Only one study, no serious inconsistency	Not serious indirectness	none	40	10	0 versus not reported	VERY LOW	CRITICAL

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