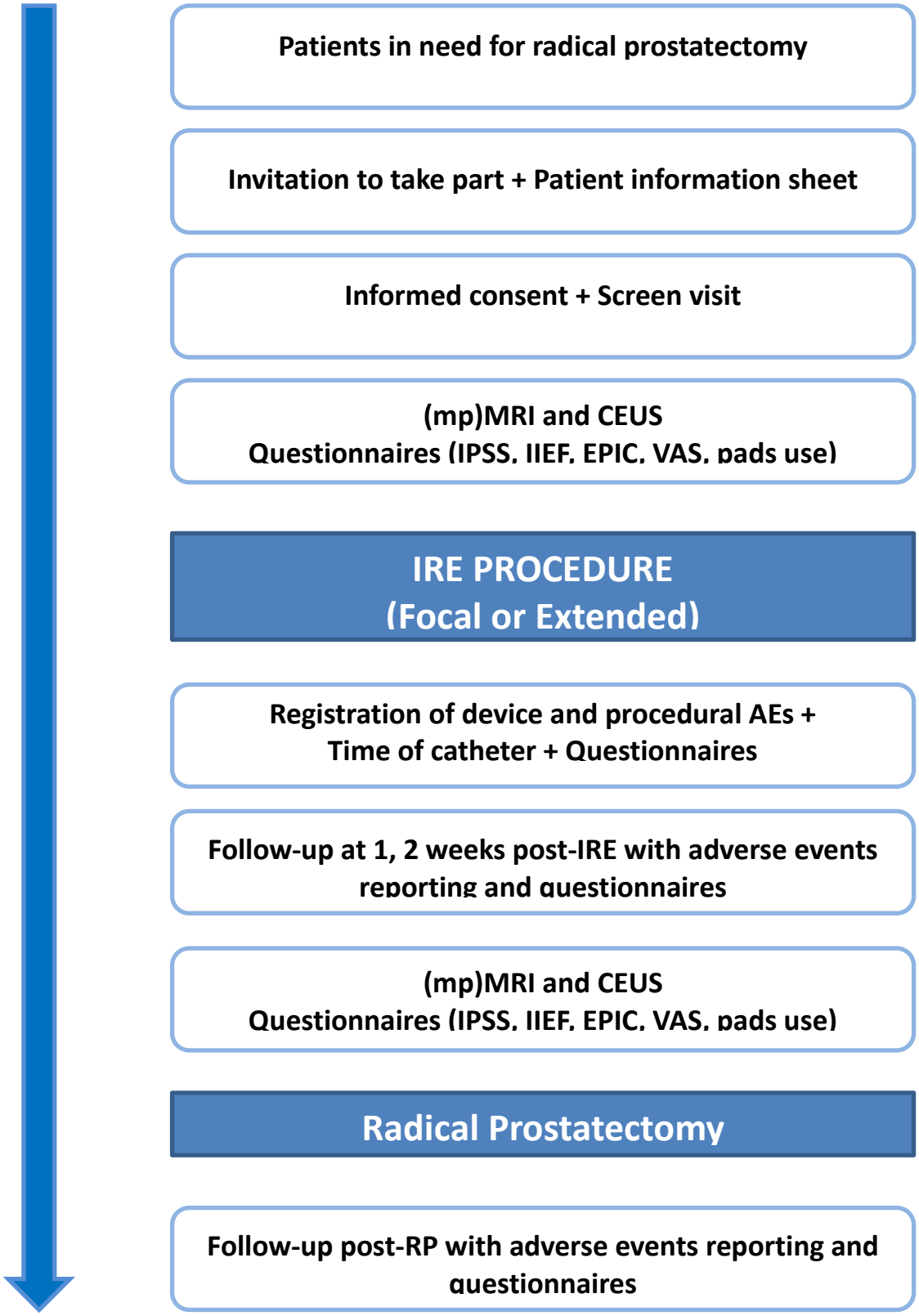
Appendix 1 Flowchart



Appendix 2 Risks of treatment

Hazard	Potential Effect(s)	Mitigation
General anesthesia (procedural)	Aspiration-infection Pulmonary compromise-ARDS Urinary retention, suprapubic catheterization Paralysis Coma Death	Supervision by trained anesthesiologist Intra-operative monitoring Pre-op history and physical exam
Muscle Blockade (procedural)	Extended anesthesia (too much blockade) Insufficient anesthesia—pain. Toxicity (If the organ that metabolizes the muscle block has compromised function)	Pre-op history and physical exam Selection of appropriate agents
Cardiac Arrhythmia (both procedural and device, unlikely from device due to distance)	Acute decrease in BP Fibrillation Cardioversion Death	Anesthesia monitoring History and physical exam Availability of treatment drugs and cardioversion equipment; ECG monitoring an procedure pacing
Multiple Prostate Biopsies (procedural)	Bleeding Infection Hematoma Pain Tumour seeding along needle tract	Biopsy technique and physician training
IRE electrode needles placed in or through sensitive structures. (Foreseeable misuse)	Sharp trauma / perforation of structures. (Blood vessels, nerves, urethra, bowel, bladder). Bleeding Infection Pain	Physician training; product labeling

Hazard	Potential Effect(s)	Mitigation
Insufficient Muscle Blockade (procedural)	Muscle strains or damage. Electrodes moved out of position. Disruption of drapes (contamination of sterile field) Trauma (to pt and medical staff) from flailing limbs	Choice of agent and dose Patient observation Physician training
Vascular Dissection (device)	Nerve damage Hematoma Surgical intervention Transfusion Death	Proper positioning and imaging guidance Physician training
Perforation (device)	Infection Fever Sepsis Coagulopathy Death	Proper positioning and imaging guidance Physician training
Hemorrhage (device)	Hematoma Surgical intervention Transfusion Increased recovery time Death	Proper positioning and imaging guidance Physician training Observation of patient during procedure
Lack of Sterile Technique/Breach of Sterile Field (procedural)	Infection Abscess Fever Sepsis Coagulopathy Death	Inspection of device packaging prior to use Sterilization and package integrity validation
ECG (EKG) Disruption after pulsing (2-3 sec)	Delayed intervention (can substitute arterial pulse until ECG returns)	Validation of ECG pacing and interface if used

Hazard	Potential Effect(s)	Mitigation
Tumour Recurrence (device)	Medical treatment Surgical treatment Death	Proper procedure planning Imaging to determine completeness of ablation Retreatment
Tumour Seeding (procedural)	Spread to other organs Medical & surgical intervention Death	Proper technique for needle placement; avoidance of unnecessary needle placements; procedure planning
Nerve Damage (device)	Erectile Dysfunction	Nerve sparring nature of IRE; placement of needles and conduct of procedure using appropriate imaging observation
Acute or Sub-acute Vascular Damage (device)	Infarction /necrosis of non-targeted prostate tissues	Pre-procedure planning Physician training Use of imaging for guidance
Injury to Prostatic Urethra or External Sphincter (device)	Urinary incontinence Impotence Surgical repair Lifestyle changes	Pre-procedure planning Physician training Use of imaging for guidance
Urethro-rectal Fistula (both procedural or device)	Pain Fever Abscess formation Infection, sepsis Surgical repair	Pre-procedure planning Physician training Use of imaging for guidance
Rectal Tear/ Perforation (from TRUS guided biopsy or Endorectal MRI coil) (procedural)	Pain Fever Abscess formation Infection, sepsis Surgical repair	Pre-procedure planning Physician training Use of imaging for guidance

Hazard	Potential Effect(s)	Mitigation
Postoperative Hemorrhage (device)	Blood transfusion Pain, Hematoma Medical/surgical intervention Death	Pre-procedure planning Physician training Use of imaging for guidance Avoidance of unnecessary needle insertion

Appendix 3 DMC charter

Objective of the study
Primary Objectives:
1. To determine if complete ablation of the specified targeted ablation zone is achieved as measured by histopathology assessment.
2. To determine if the IRE ablation procedure is safe as measured by the composite number of procedural, device and post procedural adverse events measured with the CTCAE proforma.

Secondary Objectives:
1. To determine if procedural side effects associated with current treatments for prostate cancer, mainly incontinence, erectile dysfunction and bowel damage are avoided as measured by the validated prostate cancer scores –EPIC, IIEF-5 and IPSS or time of CAD required.
2. To determine patient satisfaction and comfort measured by Patient Satisfaction Questionnaire, post procedural pain management and pain scores, time to ambulation, length of hospital stay.
3. To determine accurateness of ablation zone detection by MRI/CEUS.

Type of study

☐ Monocenter (AMC)

☒ Multicenter Number of sites, including AMC: *2*

Name principal investigator participating center 1: Prof. J.J.M.C.H. de la Rosette MD PhD
Department, Hospital: Department of Urology, Academic Medical Center, University of Amsterdam

Name principal investigator participating center 2: IM Varkarakis MD PhD,
Department, Hospital: Medical University, 2nd Department of Urology, University of Athens

Planned number of participants (total and per center): 16 in total.
AMC: 8
Sismanoglio: 8

Planned period of observation
Moment of inclusion of first patient included: *01-01-2013*
Moment of follow-up of last patient included: *31-12-2015*

Risk of the study

☐ negligible risk

☒ moderate risk

☐ high risk

Motivation of risk assessment:

Potential Hazards and Effects of the NanoKnife System	**Potential Effect(s)**
Excessive energy delivery	Muscle contraction, Burn, Damage to critical anatomical structure Unintended tissue gets ablated, Bradycardia – hypotension, Vagal stimulation – asystole, Electrical shock, Myocardial infarction, Stroke, Death
Insufficient/ no energy delivery	Ineffective ablation, No ablation
Unintended mains or patient circuit voltage exposure to patient or user	Electrical shock
Incorrect timing of pulse delivery	Transient arrhythmia, Prolonged arrhythmia, Stroke, Death
Unintended interference with implanted electronic devices or implanted devices with metal parts	Pacing inhibited, Inappropriate shock from ICD, Myocardial infarction, Stroke, Death
Unexpected movement of the device and displacement of the electrodes	Hypotension, Damage to critical anatomical structure Pneumothorax, Unintended mechanical perforation, Hemorrhage, Unintended tissue gets ablated, Electrical shock, Death
Sterile barrier breach	Infection, sepsis

Scope of the charter

1. Aims of the DSMB

The DSMB will act in an independent, expert and advisory capacity to monitor participant safety, and evaluate the efficacy and the overall conduct of the study.

2. Responsibilities of the DSMB

- *Monitor safety data on a regular basis and, if required, on ad hoc basis to guide recommendation for continuation of the study or early termination because of clear harm.*
- *Monitor efficacy data on a regular basis to guide recommendations for continuation of the study or early termination because of clear harm or futility.*
- *Evaluate the overall conduct of the trial, including*
    - *monitoring of compliance with the protocol by participants and investigators*
    - *monitoring of recruitment figures and losses to follow-up*
    - *monitoring planned sample size assumptions*
    - *reports on data quality*
    - *reports on completeness of data*
    - *monitoring of continuing appropriateness of patient information*

3. DSMB membership

3.1 Confidentiality

DSMB members will not share confidential information with anyone outside the DSMB, including the Principal Investigator. Strict confidentiality is also expected from the independent statistician who produces the interim report(s) for the DSMB. The DMSB members should store relevant documents safely after each meeting.

4. Timing and purpose of meetings

An initial meeting of the DSMB will be held prior to any participant enrollment in order for the DSMB members to fully understand the research protocol, to review and approve the DSMB charter, to review the monitor plans for safety and efficacy data, and to review the statistical methods, including stopping rules.
Subsequent DSMB meeting(s) will be held according to the following schedule:

Timeline	*Type of data by treatment group*
Prior to participant enrollment.	*Explanation research protocol, reviewing the monitor plans for safety and efficacy data, and to review the statistical methods, including stopping rules. Reviewing and approving the DSMB charter.*
*When **enrollment** is completed on first participant*	*Relevant baseline data, protocol violations, enrollment data, loss to follow-up, safety data, efficacy data.*

*When **follow-up** is completed on first participant*	*Idem*
*When **enrollment** is completed on second participant*	*Idem*
*When **follow-up** is completed on second participant*	*Idem*
*When **enrollment** is completed on first eight participants*	*Idem*
*When **follow-up** is completed on first eight participants*	*Idem*
When enrollment is completed on sixteen participants	*Idem*
*When **follow-up** is completed on sixteen participants*	*Safety of data*

4. Meeting format

Open session. This session will be attended by the Principal Investigator, representatives of the involved investigators, and the independent statistician. During this meeting the study team will provide general study information. The open session also provides the DSMB the opportunity to query the study team about issues that have arisen during their review of the data.

Closed session. In addition to the material available in the open session, the closed session will include safety and efficacy data by treatment groups. Only DSMB members will be present. The independent statistician who has produced the DSMB interim report will also participate in the DSMB meeting(s) and will guide the DSMB through the report.

Ad hoc meetings. An ad hoc meeting of the DSMB may be called at any time by the Principal Investigator or DSMB chair if immanent participants' safety issues arise.

5. Meeting minutes

Meeting minutes will be kept for each meeting of the DSMB. The minutes of the open session will be prepared by the Principal Investigator and approved by the DSMB members. The minutes of the closed session will be prepared by the DSMB chair and approved by the DSMB members. The Principal Investigator and DMSB members should store the minutes safely.

6. Preparation of interim report(s) to DSMB

The interim report(s) will consist of an Open Session Report and a Closed Session Report.

The Open Session Report will provide non-confidential, aggregated information in terms of overall study progress, enrollment, lost to follow-up, study compliance, data quality, baseline characteristics and (adverse) outcome events. The open report will be prepared by the Principal investigator (or independent statistician / statistical data analyst).

The Closed Session Report will (additionally) provide safety and efficacy data by treatment group. The closed report will be prepared by the independent statistician and will be distributed to the DSMB at least 1 week prior to the scheduled meeting. The DSMB will also be provided with the randomization list in order to have access to individual treatment assignment Ad hoc

data summaries may be prepared upon request by the DSMB to address a specific safety (and/or efficacy) concern.

6.1 Independent statisticians

The independent statistician will prepare the data and conduct the interim analysis/analyses. As the independent statistician reporting the data to the DSMB is not a member of the study group all efforts will be made by the Principal Investigator to ensure both that the independent statistician is familiar with the design, setting, and objectives of the trial, and has access to the database to provide insightful analyses responsive to the DSMB's needs.

7. Decision making

After considering the information in the interim report, the DSMB could give the following recommendations:

- *continue the study according to the study protocol*
- *continue the study with modifications to conduct or design*
- *discontinue the study due to clear harm*
- *discontinue the study due to futility*
- *discontinue the study because completion of the study is not feasible*

The justifications for a recommendation to terminate the study due to clear harm will be based on data showing a notably increase of (serious) adverse events in the intervention group (page 41).

8. DSMB report(s) to the Principal Investigator

Following each DSMB meeting, the DSMB will send a confidential report to the Principal Investigator within 2 weeks of each meeting. The report contains sufficient information to explain the rationale behind any specific recommendation by the DSMB. If the Principal Investigator accepts the recommendations, he will be responsible for implementing the concerning actions. If the Principal Investigator rejects the DSMB's recommendations, he will provide the DSMB with a written explanation of their decision and supporting rationale within 10 working days. If the DSMB has recommended that the study should be stopped but the Principal Investigator decides to continue the study, the investigator will inform immediately the METC and all concerned regulatory authorities of its decision to continue the study despite the DSMB's recommendation.