MSAC Application 1794

Irreversible Electroporation (IRE) for Prostate Tumour Tissue in patients with Prostate Cancer

PICO Set

Population

Describe the population in which the proposed health technology is intended to be used:

Ablation via irreversible electroporation (IRE) is proposed to be used in patients with intermediate risk prostate cancer as well as a salvage option for patients who have previously undergone radiation therapy unsuccessfully, have a recurrence and are not candidates for radical prostatectomy.

Australia has one of the highest incidence rates of prostate cancer. The population treated are men, most often between the ages of 55-75. Prostate cancer could be identified through initial prostate examination or investigations of PSA (prostate specific antigen) level initiated by a primary physician. Should prostate cancer be suspected, the patient would be referred to a urologist for additional investigations. The cancer is confirmed and graded by biopsy and imaging, and subsequently a treatment plan is developed. All newly diagnosed patients should be discussed by a multidisciplinary team (MDT) before beginning treatment.

Advances in imaging, have led to an increase in early detection and management of prostate cancer with and a focus on minimising harm and reducing overdiagnosis and overtreatment (Williams et al. 2022)

Specify any characteristics of patients with, or suspected of having, the medical condition, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian healthcare system in the lead up to being considered eligible for the technology:

Irreversible electroporation can be used as a treatment option for two groups of prostate cancer patients-

- As a primary, focal treatment for patients with a localised low to intermediate grade prostate cancer ISUP 2 or 3 (Gleason score 3+4=7 or 4+3=7) or a high-risk, low-grade cancer (Gleason 3+3=6) as assessed by an MDT.
- As a salvage treatment option for prostate cancer patients who have previously undergone radiation therapy and have had a recurrence. These patients may not be suitable for surgery and have limited other treatment options.

The tumor in these patients should be localised and should be thoroughly evaluated with high quality transperineal targeted and mapping biopsies as well as visible on imaging. There should be good co-registration between the imaging and the tissue biopsy, and the patient must have a life expectancy greater than 10 years.

Within the Australian system, most prostate cancers are suspected based on routine informed PSA (prostate specific antigen) test. When results are elevated or abnormal, the patient is referred to a specialist urologist who evaluate the patient and investigate further, if appropriate using multiparametric MRI. At this stage, if there is abnormality on the MRI, patients would undergo a transperineal biopsy of the prostate to confirm if cancer is present and graded using the biopsy findings. Then, a full discussion with the urologist as well as a multidisciplinary medical team occurs

to discuss potential treatment options, including radical prostatectomy, radiotherapy, brachytherapy and focal therapy including irreversible electroporation. In discussion of irreversible electroporation, the clinical and psychosocial needs of the patient are discussed, as well as the potential to preserve genitourinary and sexual function.

Provide a rationale for the specifics of the eligible population:

Irreversible electroporation (IRE) has demonstrated safety and efficacy in treating patients with localised, focal prostate cancer of intermediate risk ISUP 2 or 3 (Gleason score 3+4=7 or 4+3=7) or high-risk, low-grade cancer (Gleason 3+3=6) (Blazevski et al. 2019). IRE offers an alternative to whole gland treatment. Whole gland treatment of prostate cancer is associated with potential quality of life side effects including, but not limited to, urinary incontinence, impotence and radiation toxicity to the bowel/bladder (Yaxley et al. 2022). Management of intermediate grade prostate cancer with focal therapy aims to minimise these quality-of-life complications associated with whole gland therapy, while simultaneously decreasing the risk of prostate cancer progression (Yaxley et al. 2022; van den Bos et al. 2017). The initial focal therapy programs have concentrated on management of low and intermediate risk prostate cancer, as this cohort has a low probability of prostate cancer specific mortality within a decade of diagnosis, even when treated with an initial approach of active surveillance (Yaxley et al. 2022). Active surveillance (AS) can be offered for low-risk prostate cancer however, the observational approach can impose a heavy burden on the patient (Flegar et al. 2022).

IRE may also be used as a salvage option for patients with recurrent prostate cancer post radiation therapy (external beam radiotherapy or brachytherapy) as an alternative to whole gland salvage treatments such as radical prostatectomy and brachytherapy. Surgical treatment of radio-recurrent prostate cancer is technically challenging for the Urologist due to the scarred tissue changes from the radiation treatment. Blazevski (2019) reported biochemical recurrence rates of this patient group between 28% and 93%, postintervention incontinence rates of between 5.4% and 67%, erectile dysfunction rates ranging from 23% to 100% and a significant incidence of high-grade adverse events, e.g. rectourethral fistula in 1–5.3% of patients. IRE aiming to achieve local oncological control and reduce the risk of genitourinary side effects associated with other treatment options.

IRE is offered as an outpatient procedure in the day surgery centre and requires only one week or less of time away from work or routine daily activities. The ability to preserve genitourinary function and sexual function is of importance clinically and for health-related quality of life. The benefits are well studied and published in peer-reviewed journals. Additionally, in the eligible population, treatment with IRE can offer cost savings to the patient as well as to Medicare, driven by reduced complications and time away from work, as well as promising cancer control over time.

Are there any prerequisite tests?
Yes

Are the prerequisite tests MBS funded?
Yes

Provide details to fund the prerequisite tests: not applicable

Intervention

Name of the proposed health technology:
The NanoKnife System for irreversible electroporation, multiprobe, percutaneous

Describe the key components and clinical steps involved in delivering the proposed health technology:

The patient is put under general anesthesia and intubated, then placed in dorsal lithotomy. A foley catheter is inserted. The scrotum is elevated and the perineum is prepped. Using transrectal ultrasound imaging guidance, the physician places IRE electrodes (between 3-6 electrodes depending on the lesion size, shape and location) to bracket the intended ablation area. Electrodes are placed parallel to each other at least 1cm apart, with attention to urethra, the neurovascular bundle, urinary sphincter and rectum. Once the electrodes are placed and anesthesia is determined sufficient to suppress muscle twitch, the physician verifies the IRE electrodes are placed as intended to achieve ablation of targeted tissue and initiates electroporation. The electroporation cycles between the probe pairs until 90 pulses per electrode pair are achieved. During the ablation, the physician is monitoring the resistance changes between electrodes to assure tissue destruction. They are monitoring the patient cardiac status. They are also monitoring the ablation zone via imaging. When IRE multiprobe treatment is complete, the patient is extubated, electrodes are removed, and surgical site dressings administered. The patient is moved to a recovery area until stable and safe to be discharged home.

Identify how the proposed technology achieves the intended patient outcomes:

IRE uses non-thermal electrical pulses to create nanopores in the cell membrane of tumors. As a function of field amplitude and duration, permeabilisation can be either reversible or irreversible. In the case of IRE, after delivering high voltage pulses above a sufficient threshold, the cells within the electrical field are irreversibly damaged. IRE performed with the NanoKnife System is a multi-needle procedure using three to six monopolar electrodes inserted into the target tissue. The applied electric field disrupts the cellular membrane allowing for an uncontrolled influx of calcium ions. This leads to cell death followed by phagocytosis, the body's natural mechanism for clearance of cellular debris in a matter of weeks which mimics the process of natural cell death.

Through its unique mechanism of action, structures mainly formed by proteins such as vascular elastic and collagenous structures and peri-cellular matrix proteins are not damaged by IRE. This leads to the preservation of structural scaffoldings of vessels and nerve bundles. IRE with accurate mapping and image-based guidance allows for precisely targeted tissue destruction. The primary use of IRE ablation is for tumors that are adjacent to or surrounding critical structure. With other types of therapy, these structures are destroyed due to radiation or surgical damage. Radiation therapies do not fully discriminate which proteins or DNA to destroy. Thus, all protein structures and cells with DNA can be damaged with the use of current radiation techniques and other radical procedures.

IRE provides the ability to perform precise ablations that result in destruction of the tumors. The protective nature of IRE compared to other treatment options results in good cancer control with lower risk of the common side effect of other treatments. Side effects that are common in treatment of prostate cancer include erectile dysfunction, nerve damage, urinary or faecal incontinence, depression and loss of work. Using IRE, many of these side effect are avoided or minimised. The NICE Guidance (2023) for use of irreversible electroporation notes that the treatment is found to be safe and effective. Peer-reviewed published data from Australia demonstrates favourable clinical and health-related quality of life outcomes for patient who receive IRE (Scheltema et al. 2019; Blazevski et al 2023).

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?
Yes. The current published literature for IRE in treatment of prostate cancer includes patients treated using The NanoKnife System.

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

Other multi-probe IRE devices may provide similar outcomes, though they do not have the body of literature to prove it at this time. These devices are not TGA certified and are not available in Australia.

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):
No

Provide details and explain:
There would be a need to assure adequate training of the urologists who intend to perform the procedure. Since the procedure offers demonstrated safety and efficacy in treating the identified population and there are potential clinical benefits and cost savings in the short and long term as compared to clinical alternatives for the defined population, the only limit suggested is additional evaluation of appropriateness for patients who may be dependent on a pacemaker. Because irreversible electroporation delivers electrical pulses, the pacemaker may be a contraindication.

If applicable, advise which health professionals will be needed to provide the proposed health technology:
IRE is provided by urologists or urologic oncologists.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:
Not applicable.

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:
Routine PSA screening in men is standard of care and is performed by general practitioners. If there is suspicion of cancer from the PSA screening or on the digital rectal exam, the general practitioner would refer the patient to the urologist.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?
Yes.

Provide details and explain:
The healthcare professional would have training in urology or urologic oncology. Additionally, the physician would have device specific training for providing irreversible electroporation. The device training may occur during the formal urology training, or may be completed through a course led by proctors with extensive experience using the device. Once the clinical mentor feels the urologist new to irreversible electroporation has sufficient knowledge and skills, generally requiring 5 cases of mentoring, the urologist new to providing the procedure would be able to perform the procedure on their own.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

(Select all relevant settings) – add additional settings if relevant in Australia

☐ Consulting rooms
☒ **Day surgery centre**
☐ Emergency Department
☐ Inpatient private hospital
☐ Inpatient public hospital
☐ Laboratory
☐ Outpatient clinic
☐ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

Is the proposed health technology intended to be entirely rendered inside Australia?
Yes

Provide additional details on the proposed health technology to be rendered outside of Australia:
Not applicable

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e., how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian healthcare system). This includes identifying healthcare resources that are needed to be delivered at the same time as the comparator service:

The appropriate comparators for Irreversible electroporation is radical therapy for localised prostate cancer. This includes radical prostatectomy and radiation therapy (radiotherapy and brachytherapy). These treatment options target the whole prostate gland through surgical removal or radiation treatment, unlike Irreversible electroporation which is considered focal therapy, targeting the segment of the prostate incorporating the prostate cancer lesion (Flegar et al. 2022).

Healthcare resources that need to be employed with the comparator services include:

Radical prostatectomy requires inpatient hospital stay, a DaVinci Robot and its related disposable/rental/acquisition costs, a minimum of 4 nursing and surgical support staff and much longer recovery post procedure.

Radiotherapy requires a linear accelerator as part of an MR LINAC machine that includes MRI capabilities. In requires a large number of staff including physicists and radiation technicians to set up and run the device. The 10 to 20 fractions are provided over a period of 2-4 weeks of regular visits to the radiotherapy department. In addition, prior to radiation therapy, there is often need for placement of fiducial marker seeds and spacing gel between the rectum and prostate to prepare the patient for treatment. Additionally, there is often a need to down-regulate hormones before radiotherapy can begin. Finally, disposal of radioactive waste is required.

Brachytherapy (low-dose) requires an initial day surgery for treatment planning, an overnight stay for implantation of the radioactive material, the cost of the expensive radioiodine seeds, radiation planning and the combination of a radiation oncologist and urologist to be present in theatre and using theatre facilities while the patient is treated. Finally, disposal of radiation waste is a cost.

List any existing MBS item numbers that are relevant for the nominated comparators:

- 37210
- 37211
- 37220
- 37227
- 15944
- 15940

Provide a rationale for why this is a comparator:

The comparators -radical prostatectomy and radiation therapy are the current standard treatment options for patients with Gleason 7 prostate cancer. Insignificant prostate cancer that is ISUP 1 (Gleason 6) is generally not treated and is instead managed by active surveillance, while high-grade prostate cancer (Gleason 8,9,10 or ISUP 4 and 5) require multimodal therapy and these patients would not be appropriate candidates for focal irreversible electroporation. Gleason 7 patients are classified as intermediate risk, with unifocal, localised lesion unlike multifocal lesions in high-grade prostate cancer. The comparators are current standard treatment options for these patients and target the whole gland. It is proposed that irreversible electroporation be an added option for treating this intermediate risk patient group. Management of intermediate grade prostate cancer with IRE aims to effectively treat localised prostate cancer similar to radical therapies, while offering an improved risk profile that minimises genitourinary side effects that are associated with whole gland therapy.

In regards to salvage prostate cancer patients for recurrence post radiation therapy, the standard treatment pathway for this patient group is a radical prostatectomy or further radiation therapy. For patients who are not fit for surgery or suitable for further radiation treatment, they are offered palliative ADT (androgen deprivation therapy) hormone therapy. NanoKnife may be used for these

patients as a treatment option for local control of the recurrent lesion with possibility to preserve genitourinary function.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

(Please select your response)

☐ None (used with the comparator)
☐ Displaced (comparator will likely be used following the proposed technology in some patients)
☒ Partial (in some cases, the proposed technology will replace the use of the comparator, but not all)
☐ Full (subjects who receive the proposed intervention will not receive the comparator)

Outline and explain the extent to which the current comparator is expected to be substituted:
Patients who are appropriate candidates for irreversible electroporation are a subset of the total population with intermediate risk, localised ISUP 2 and 3 prostate cancer. Focal IRE would be expected to replace the comparator treatment options in approximately 20% - 25% of the total ISUP 2 and 3 patients. As with any treatment option for prostate cancer, there is a risk of the cancer recurring. Long term data has shown that between 10% -15% of patients treated with irreversible electroporation may experience recurrent disease necessitating additional treatment (Scheltema et al. 2022). These patients may go on to have another IRE treatment or whole gland radical treatment such as prostatectomy or radiation therapy.

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☒ Health harms
☒ Resources
☒ Value of knowing

Outcome description – include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

The key outcomes in comparing focal IRE to radical therapy include:

1. Genitourinary side effects: Focal IRE has a <1% incidence of significant urinary incontinence; whereas, radical prostatectomy reports 10% incidence of significant urinary incontinence.

    - There is significant psychosocial impact of incontinence
    - Additionally, there is significant cost to treating incontinence with further therapies ranging from pelvic floor strengthening exercises to various operations including slings and artificial sphincter use.

- Overall, IRE leads to better quality of life for patients vs radical therapies and it can reduce the expenses to the patient and the care system.

2. Sexual function: Incidence of erectile dysfunction after focal IRE is between 5%-10%, whilst radical therapies report incidence of erectile dysfunction ranging from 30%-70% of patients treated.
    - This is a major impact physically and psychologically patients treated
    - The cost of treating erectile dysfunction is significant, whether from PDE5 inhibitors, penile injection therapy or penile prosthesis and psychology counselling
    - Sexual dysfunction can lead to relationship issues as well as other health impediments.

3. Resource Utilisation:
    - Focal IRE
        i. Requires a day surgery procedure which takes approximately one hour, requires a transperineal needle placement, potentially a short term foley catheter and full recovery in 1-2 days.
        ii. Patients can return to work or normal daily activities in approximately one week.
        iii. Major side effects are rare.
    - Radical Therapy – radical prostatectomy, radiotherapy or brachytherapy
        i. Treatment is provided in hospital or a radiotherapy department.
        ii. Requires extensive equipment, labor, time.
        iii. Major side effects can occur.

4. Recurrence Rate for Cancer
    - Focal IRE has a recurrence rate of 15% at 5-10 years.
    - Radical treatment options have a recurrence rate of 20% at 5-10 years.

Patients treated with focal IRE are expected to experience reduced recurrence rates and a favorable side effect profile vs the experience of patients treated with the radical therapy. For patients that do have recurrent disease, in the cohort treated with focal IRE are able to be offered a subsequent IRE procedure or a radical treatment option. If patients who were initially treated with radical therapy experience recurrence, they may be offered a focal IRE salvage procedure or another radical treatment option in combination with hormone therapy.

Non-Health Outcomes

In addition to its clinical benefits, NanoKnife IRE for focal therapy in prostate cancer generates significant non-health outcomes that positively impact patients, families, and society. The procedure's minimally invasive nature not only improves recovery times but also allows patients to maintain their roles within their families and communities with minimal disruption. This contributes to a reduced caregiving burden for families and supports better mental and emotional well-being for caregivers. The precision of the procedure minimises treatment-related morbidity, providing patients with greater confidence and peace of mind regarding their prognosis and quality of life.

Economically, quicker recovery and reduced treatment side effects mean patients can return to work sooner, preserving workplace productivity and reducing absenteeism. For retired individuals, faster recovery facilitates active engagement in volunteering, mentorship, or other community activities, contributing to social cohesion and community resilience.

From a healthcare system perspective, the availability of NanoKnife IRE enhances the reputation of Australian healthcare as a leader in adopting cutting-edge, patient-centered innovations. This may attract support for research collaborations, driving further advancements in healthcare technology. Additionally, the reduced need for long-term care associated with minimised complications lowers the burden on public and private healthcare resources, potentially resulting in cost savings that can be reallocated to other critical areas of need.

Finally, the psychological benefit of offering patients a precise, localised treatment option that preserves quality of life and avoids the broader side effects of conventional treatments, such as radical prostatectomy or radiation, cannot be overstated. This empowerment through choice and the potential for better post-treatment quality of life has a ripple effect, enhancing trust in the healthcare system and improving patient satisfaction.

Proposed MBS items

How is the technology/service funded at present? (e.g., research funding; State-based funding; self-funded by patients; no funding or payments):
Self-funded by patients

Provide at least one proposed item with their descriptor and associated costs, for each Population/Intervention:

MBS item number (where used as a template for the proposed item)	Specify MBS item number here
Category number	Category 3
Category description	THERAPEUTIC PROCEDURES
Proposed item descriptor	Prostate, Irreversible electroporation, using transrectal ultrasound guidance: (a) for a patient with: (i) Confirmed histopathological localised prostatic malignancy (ii) a Gleason score of less than or equal to 7 (Grade Group 1 to Grade Group 3) (iii) a multidisciplinary team has reviewed treatment options for the patient and assessed that focal therapy is suitable (b) performed by a urologist at an approved site
Proposed MBS fee	$1,815.35

Indicate the overall cost per patient of providing the proposed health technology	Approximately $23,000
Please specify any anticipated out of pocket expenses	NanoKnife IRE Electrodes cost between $10,000-$15,000 depending upon number of electrodes used.
Provide any further details and explain	Cost breakdown includes Urologist fee, anaesthesia, Hospital fee including consumables and NanoKnife IRE generator and electrodes This treatment could be performed a second time in case of a recurrence.

MBS item number (where used as a template for the proposed item)	
Category number	Category 3
Category description	THERAPEUTIC PROCEDURES
Proposed item descriptor	Prostate, Irreversible electroporation, using transrectal ultrasound guidance: (a) for a patient with: (i) Confirmed imaged and/or histopathological recurrent prostatic malignancy (ii) previous radiation therapy (including brachytherapy) on the prostate (iii) a multidisciplinary team has reviewed treatment options for the patient and assessed that salvage irreversible electroporation is suitable (b) performed by a urologist at an approved site in association
Proposed MBS fee	$1,815.35
Indicate the overall cost per patient of providing the proposed health technology	Approximately $23,000
Please specify any anticipated out of pocket expenses	NanoKnife IRE Electrodes cost between $10,000-$15,000 depending upon number of electrodes used.
Provide any further details and explain	Cost breakdown includes Urologist fee, anaesthesia, Hospital fee including consumables and NanoKnife IRE electrodes

Algorithms

PREPARATION FOR USING THE HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:
Patients would be required to have confirmed unifocal intermediate risk prostate cancer, Gleason 3+4 or 4+3 or evidence/history of aggressive prostate cancer at least Gleason 6. The staging is completed via biopsy of the lesion and/or use of other confirmatory imaging. All diagnosed patients should be discussed by a multidisciplinary team (MDT) for a treatment plan.

For salvage radio-recurrent patients, continuous PSA monitoring to monitor for Biochemical recurrence is a standard follow up protocol post primary radiation therapy. A rise in PSA may indicate a suspected recurrence. The patient then undergoes further investigations including biopsy and imaging to confirm the recurrence and subsequently, the patient is discussed at an MDT and a treatment plan is developed.

Is there any expectation that the clinical management algorithm before the health technology is used will change due to the introduction of the proposed health technology?

No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:
The diagnostic pathway for prostate cancer will not change due to introduction of IRE. The change to the clinical management algorithm is with full discussion of all treatment options and side effects that occur during patient consultation with the Urologist. There is also evidence from the NICE review of IRE prostate that this would yield cost benefits to patients and the healthcare system.

USE OF THE HEALTH TECHNOLOGY

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

The following healthcare resources are used in conjunction with IRE:

- general anaesthetic
- Day surgery theatre
- Transrectal Ultrasound imaging guidance
- A stepper and grid
- One to two nursing staff in addition to the physician in the day surgery unit
- Irreversible electroporation generator and electrodes.

The procedure is performed in a day surgery setting under general anaesthetic. Transrectal ultrasound imaging guidance is used for visualization of the prostate and live imaging guidance of the treatment, A stepper and grid are utilized to aid in IRE electrode placement, while the NanoKnife IRE generator is used to administer the electrical pulses into the patient for the treatment. The staff resources are required to aid the Urologist.

Explain what other healthcare resources are used in conjunction with the comparator health technology:
Comparators:

All of the options below will require psychological counselling services and will likely require treatment for incontinence and erectile dysfunction.

1. **Radical prostatectomy** requires inpatient hospital stay, a DaVinci Robot and its related disposable/rental/acquisition costs, a minimum of 4 nursing and surgical support staff and much longer recovery post procedure.
2. **Radiotherapy** requires a linear accelerator as part of an MR LINAC machine that includes MRI capabilities. In requires a large number of staff including physicists and radiation

technicians to set up and run the device. The 10 to 20 fractions are provided over a period of 2-4 weeks of regular visits to the radiotherapy department. In addition, prior to radiation therapy, there is often need for placement of fiducial marker seeds and spacing gel between the rectum and prostate to prepare the patient for treatment. Additionally, there is often a need to down-regulate hormones before radiotherapy can begin. Finally, disposal of radioactive waste is required.

3. **Brachytherapy (low-dose)** requires an initial day surgery for treatment planning, an overnight stay for implantation of the radioactive material, the cost of the expensive radioiodine seeds, radiation planning and the combination of a radiation oncologist and urologist to be present in theatre and using theatre facilities while the patient is treated. Finally, disposal of radiation waste is a cost.

Describe and explain any differences in the healthcare resources used in conjunction with the <u>proposed health technology</u> vs. the <u>comparator health technology</u>:
Focal IRE clearly requires less resources than the comparators. The drivers of the reduction in the resources for IRE are:

1. A single treatment day in a day surgery setting with Focal IRE vs inpatient hospital or repeated days of treatment with radical treatments.
2. Less staff required for focal IRE
3. Less costly device and disposables required for IRE
4. No radioactive waste to dispose of for IRE
5. Reduced recovery time and time away from work for patients treated with IRE
6. Reduced recurrence and favourable side effect profile

<u>CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY</u>

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the <u>proposed health technology</u>:

IRE post procedure care:

After IRE treatment, swelling of the immediate ablation zone would be expected, so the patient would be sent home with a foley catheter which would be in place for 2-5 days. This would be removed as an outpatient at the procedure follow up visit with the urologist. Within 6 months, a limited MRI would be done to assess status of the ablation zone and PSA screenings would be done initially at 3 month intervals. It is generally recommended that a biopsy of the treated region be performed at approximately one year post focal IRE to ensure complete clearance of disease. After year 1, relatively non-invasive monitoring would include PSA testing every 6 months and another MRI yearly.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the <u>comparator health technology</u>:

1. Radical Prostatectomy post procedure care:
   Radical prostatectomy involves a 2-3 hour operative procedure, a 2-day in hospital stay and a catheter in place for 6 days. There would be limitations on activities for 4 to 6 weeks post

procedure and ongoing management of urinary incontinence. The patient would receive training in pelvic floor exercise as well as likely sexual rehabilitation with use of PDE5 inhibitors +/- a vacuum device to help erections recover. Monitoring post surgery and hospital discharge would involve 6 monthly PSAs, with the initial PSA done at 6 weeks. The patient would have follow up visits with the urologist at 6 days, 6 weeks, 12 weeks and additionally as needed for urinary incontinence, other genitourinary issues and erectile dysfunction. The patient would then be followed after year one with relatively non-invasive monitoring including PSA testing and another MRI yearly. The potential side effects that occur will determine additional treatments and follow up visits required. For patients with ongoing incontinence or sexual dysfunction, additional medical procedures may be required in addition to pads or diapers.

2. Radiotherapy (external beam) or Brachytherapy:
   Post completion of therapy over a course of 2-4 weeks, which is often associated with synchronous antiandrogen therapy to down-regulate hormones, the follow up is dictated by the side effects of the therapy for the individual patient. Urinary incontinence and other genitourinary issues may require regular visits, medications or additional medical procedures, in addition to pads or diapers. Radiation therapy can cause gastrointestinal side effects with may also require regular review, medications and occasionally invasive treatment such as laser therapy to the rectum or hyperbaric oxygen therapy. While the incidence rate of some of these complications are generally low, these can result in significant grade 3 or 4 adverse events.

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:

IRE offers a shorter initial recovery period than its comparators, with reduced risk of genitourinary complications. This affects the healthcare resources post procedure. As IRE is considered focal therapy, targeting a lesion of the prostate, short-term continued monitoring of the patient is required with initially PSA screenings, imaging and biopsy. For long term follow up, only PSA screening and MRI if required .

Radical prostatectomy involves the removal of the prostate. These patients would undergo a longer recovery period from the surgery, but long term follow up, will not require continued monitoring of their prostate. This patient group has a higher risk of genitourinary complications. If required, these patients would be dependent upon healthcare resources for ongoing incontinence or sexual dysfunction, and additional medical procedures may be required in addition to pads or diapers.

Radiation Therapy also requires continued PSA monitoring, similar to IRE patients. These patients may also require continuous ADT hormone therapy. The follow up for this patient group is dictated by the side effects of the therapy for the individual patient. Urinary incontinence and other genitourinary issues may require regular visits, medications or additional medical procedures, in addition to pads or diapers, similar to radical prostatectomy patient follow up.

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Abbreviations: IRE - Irreversible Electroporation, ISUP - International Society of Urological Pathology, MDT - multi-disciplinary team meeting

Figure 1: Proposed clinical management algorithm after the proposed listing

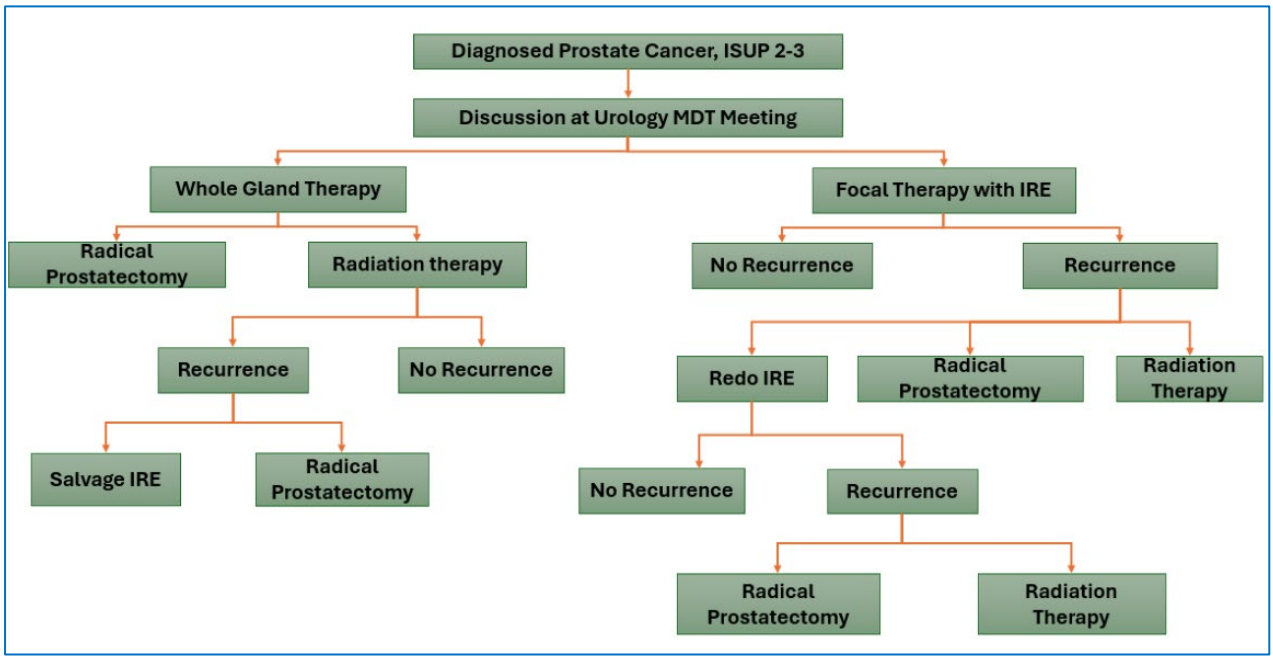
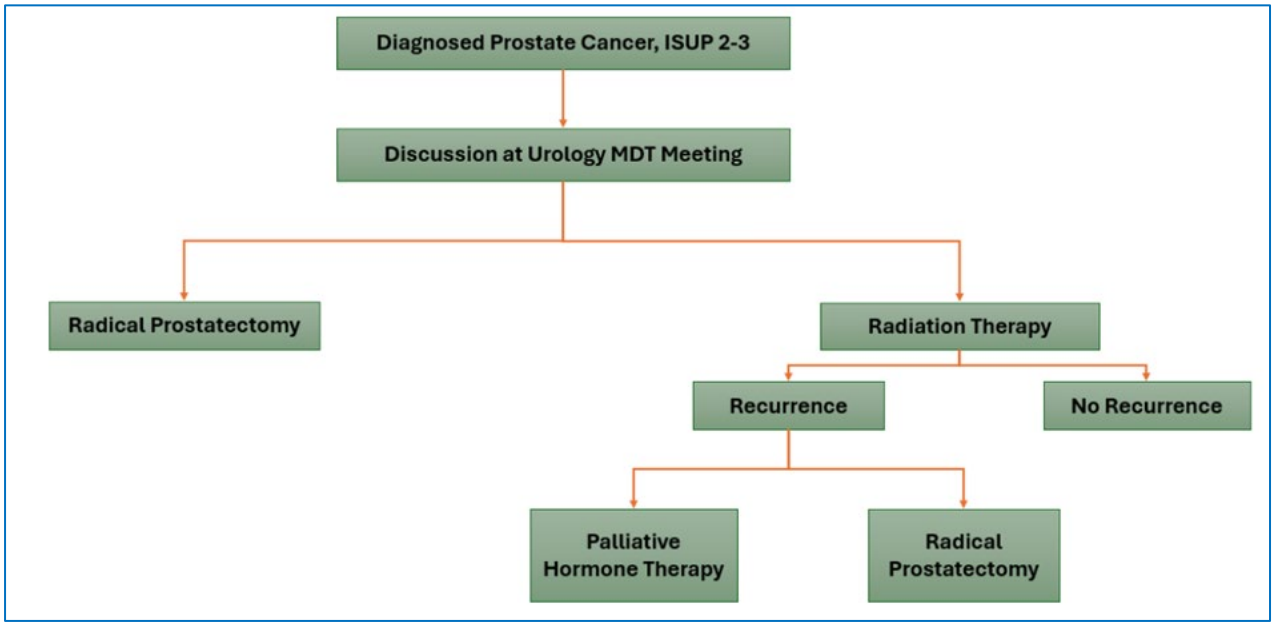


Figure 2: Current clinical management algorithm in the absence of public funding for the proposed medical service



Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

☒ Superior
☒ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:
Claim: IRE has a lower risk of genitourinary side effects, and similar oncological outcomes along with decreased treatment related morbidity and cost, in comparison to the comparators

Rationale: the comparator, radical therapies for treatment of intermediate risk prostate cancer ISUP 2 or 3 (Gleason 3+4=7 or 4+3=7), has higher resource utilisation, higher morbidity, similar recurrence and a worse side effect profile for genitourinary and sexual function outcomes.

Said differently, in the intermediate risk prostate cancer population ISUP 2 or 3 (Gleason 3+4=7 or 4+3=7) focal IRE has lower resource utilisation and recovery time, lower morbidity, similar recurrence and a better side effect profile for genitourinary and sexual function outcomes.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?
IRE offers lower rates of incontinence, of erectile dysfunction and of reported depression with lower resource utilisation and faster patient recovery time than the comparator. Oncological control of the cancer is non-inferior.

Identify how the proposed technology achieves the intended patient outcomes:
IRE uses non-thermal electrical pulses to create nanopores in the cell membrane of tumors. As a function of field amplitude and duration, permeabilization can be either reversible or irreversible. In the case of IRE, after delivering high voltage pulses above a sufficient threshold, the cells within the electrical field are irreversibly damaged. IRE performed with the NanoKnife System is a multi-needle procedure using three to six monopolar electrodes inserted into the target tissue. The resulting electric field disrupts the cellular membrane allowing for an uncontrolled influx of calcium ions. This leads to cell death followed by phagocytosis, the body's natural mechanism for clearance of cellular debris in a matter of weeks which mimics the process of natural cell death.

Through its unique mechanism of action, structures mainly formed by proteins such as vascular elastic and collagenous structures and peri-cellular matrix proteins are not damaged by IRE. This leads to the preservation of structural scaffoldings of vessels and urethra. IRE with accurate mapping and image-based guidance allows for precisely targeted tissue destruction. The primary use of IRE ablation is for tumors that are adjacent to or surrounding critical structures.

IRE provides the ability to perform precise ablations that result in destruction of the tumors. The protective nature of IRE as compared to other treatment options results in good cancer control with lower risk of many of the common side effect of other treatments. Side effects that are common in treatment of prostate cancer include erectile dysfunction, nerve damage, urinary or fecal incontinence, depression and loss of work. Using IRE, many of these side-effects are avoided or minimized.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management? Yes

A change in health outcome? Yes

Other benefits? Yes

Please provide a rationale, and information on other benefits if relevant:
The IRE side-effect profile has reduced morbidity – lower incidence of incontinence, lower incidence of erectile dysfunction, improved health-related quality of life, reduced depression, quicker recovery and reduced recurrence. The clinical management of patients receiving focal IRE can be more efficient with a lower burden on the health resources. The positive health outcomes and other benefits like quicker recovery, less depressive symptoms and reduced out of pocket costs and retained relationships can be realised in comparison to the comparators.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

(Please select your response)

More costly
☐ Same cost
☒ Less costly

Provide a brief rationale for the claim:

The costs for IRE is less than the comparators. Surgical resection and Radiation therapy incur greater costs when taking into account the following factors-

-Higher surgeon fee required for a higher technical procedure of radical prostatectomy and a overall longer procedure time

- Pathologist fee required for surgical resection for speciman histopathology anaylsis

- Radiation oncologist fees, additional specialty required for the radiation therpay procedure.

- Increased hospital fees are required including admission costs for these patients while IRE can be performed on an outpatient basis

- Captial fee of the machinery required for radical prostatectomy e.g DaVinci Robot and MR LINAC machine for radiation therapy.

- Radical prostatectomy and radiation therapy also have a higher risk of treatment complications. These associated fees also contribute to greater overall procedure cost.

If your application is in relation to a specific radiopharmaceutical(s) or a set of radiopharmaceuticals, identify whether your clinical claim is dependent on the evidence base of the radiopharmaceutical(s) for which MBS funding is being requested. If your clinical claim is dependent on the evidence base of another radiopharmaceutical product(s), a claim of clinical noninferiority between the radiopharmaceutical products is also required.

Not applicable.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology.

	Type of study design*	**Title of journal article or research project** (including any trial identifier or study lead if relevant)	**Short description of research** (max 50 words)**	**Website link to journal article or research** (if available)	**Date of publication*** **
1.	Prospective, non-randomized, clinical trial	A Description and Safety Overview of Irreversible Electroporation for Prostate Tissue Ablation in Intermediate-Risk Prostate Cancer Patients: Preliminary Results from the PRESERVE Trial **ClinicalTrials.gov Identifier: NCT04972097**	Prospective, non-randomized, pivotal clinical trial evaluating the safety and effectiveness of IRE using the NanoKnife System for prostate tissue ablation in patients with intermediate-risk prostate cancer.	https://www.mdpi.com/2072-6694/16/12/2178	2024
2.	Prospective observational study	A multi-center international study to evaluate the safety, functional and oncological outcomes of irreversible electroporation for the ablation of prostate cancer **ClinicalTrials.gov Identifier: NCT02255890**	Multicenter, international, prospective observational study evaluating the safety, functional outcomes, and oncological efficacy of IRE for the treatment of localized prostate cancer.	https://www.nature.com/articles/s41391-023-00783-y	2024
3.	Systematic review and meta-analysis	Irreversible Electroporation for the Focal Treatment of Prostate Cancer: A Systematic Review	Systematic review evaluating the safety, oncological, and functional outcomes of IRE	https://wjmh.org/DOIx.php?id=10.5534/wjmh.240012	2024

			as a focal treatment for localized low- or intermediate-risk prostate cancer.		
4.	Prospective study	Long-Term Oncologic Outcomes of Image-Guided Irreversible Electroporation for Localized Prostate Cancer **EA4/052/13**	Single-center prospective study evaluating the long-term oncological outcomes of focal MRI–transrectal ultrasound fusion–guided IRE for localized prostate cancer, focusing on metrics such as failure-free survival, metastasis-free survival, and prostate cancer-specific survival over a 5-year period.	https://link.springer.com/article/10.1007/s00270-024-03826-6	2024
5.	Prospective study	Targeted Ablation Using Ultrasound-Guided Irreversible Electroporation of Index Tumors (TARGET Study): Prospective Development Study Evaluating Safety, Patient-Reported Outcomes, and Oncologic Efficacy **IRB No. 16-1430**	Single-center prospective pilot study evaluating the safety, patient-reported functional outcomes, and short-term oncological efficacy of focal IRE as a primary treatment for intermediate-risk prostate cancer.	https://www.auajournals.org/doi/abs/10.1097/UPJ.0000000000000666	2024
6.	Prospective observational study	Irreversible electroporation of localised prostate cancer downregulates immune suppression and induces	Single-center prospective observational study investigating the systemic immune responses induced by focal IRE	https://bjui-journals.onlinelibrary.wiley.com/doi/10.1111/bju.16496?af=R	2024

		systemic anti-tumour T-cell activation –IRE-IMMUNO study **SVH2020/ETH00157**	compared to robot-assisted radical prostatectomy in patients with localized intermediate-risk prostate cancer.		
7.	Randomized study	A Multicenter, Randomized, Single-blind, 2-Arm Intervention Study Evaluating the Adverse Events and Quality of Life After Irreversible Electroporation for the Ablation of Localized Low-intermediate Risk Prostate Cancer **ClinicalTrials.gov Identifier: (NCT01835977)**	Multi-center, randomized, single-blind, two-arm intervention study evaluating the adverse events, quality of life, and oncological outcomes of focal versus extended IRE for the ablation of localized low-to-intermediate-risk prostate cancer.	https://www.auajournals.org/doi/10.1097/JU.0000000000003051	2023
8.	Retrospective study	Focal Irreversible Electroporation for Localized Prostate Cancer – Oncological and Safety Outcomes Using mpMRI and Transperineal Biopsy Follow-Up	Retrospective study of IRE treatment for prostate cancer that includes both primary and salvage treatment, focusing on oncological and safety outcomes using multiparametric and transperineal biopsy follow-up.	https://www.dovepress.com/focal-irreversible-electroporation-for-localized-prostate-cancer--onco-peer-reviewed-fulltext-article-RRU	2023
9.	Randomized Clinical Trial	Effect of Focal vs Extended Irreversible Electroporation for the Ablation of Localized Low- or Intermediate-Risk Prostate	Randomized multi-center clinical trial evaluating the comparison of oncological control and quality-of-life outcomes of focal versus	https://jamanetwork.com/journals/jamasurgery/fullarticle/2800978	2023

		Cancer on Early Oncological Control A Randomized Clinical Trial **ClinicalTrials.gov Identifier: NCT01835977**	extended IRE ablation therapy in men with localized low- or intermediate-risk prostate cancer.		
10.	Retrospective study	Median 4-year outcomes of salvage irreversible electroporation for localized radio-recurrent prostate cancer Some patients in this study were treated as part of the prospective FIRE trial **(ACTRN12617000806369)**	Retrospective study of prospectively and retrospectively acquired data evaluating the mid-term oncological and quality-of-life outcomes of salvage IRE for localized radio-recurrent prostate cancer.	https://bjui-journals.onlinelibrary.wiley.com/doi/full/10.1111/bju.15948	2023
11.	Prospective phase II study	Focal Therapy of Prostate Cancer Index Lesion With Irreversible Electroporation. A Prospective Study With a Median Follow-up of 3 Years **IRB No. ESTU-0028/13/UN0021**	Single-center prospective phase II study evaluating the oncological, safety, and quality-of-life outcomes of focal IRE for the treatment of localized prostate cancer.	https://www.auajournals.org/doi/abs/10.1097/JU.0000000000002970	2023
12.	Retrospective review of prospective study	Focal therapy for prostate cancer with irreversible electroporation: Oncological and functional results of a single institution study	Retrospective review of prospective study evaluates the oncological and functional outcomes of focal IRE for prostate cancer, including both primary and salvage treatments, conducted at a single institution.	https://icurology.org/DOIx.php?id=10.4111/icu.20210472	2022

13.	Retrospective study	Outcomes of salvage radical prostatectomy after initial irreversible electroporation treatment for recurrent prostate cancer	Retrospective multi-center study examining the safety, feasibility, and medium-term oncological and functional outcomes of salvage radical prostatectomy after initial treatment with IRE for recurrent localized prostate cancer.	https://bjui-journals.onlinelibrary.wiley.com/doi/10.1111/bju.15759	2022
14.	Prospective observational study	Median 5-year outcomes of primary focal irreversible electroporation for localised prostate cancer	Prospective study evaluating the median 5-year oncological and functional outcomes of primary focal IRE as a treatment for localized prostate cancer.	https://bjui-journals.onlinelibrary.wiley.com/doi/10.1111/bju.15946	2022
15.	Prospective study	Salvage irreversible electroporation for radio-recurrent prostate cancer – the prospective FIRE trial **ACTRN12617000806369**	Prospective multi-center clinical trial investigating the safety, functional, and oncological outcomes of salvage IRE for men with radio-recurrent localized prostate cancer following previous radiotherapy.	https://bjui-journals.onlinelibrary.wiley.com/doi/abs/10.1111/bju.15947	2022
16.	Retrospective study	Focal ablation of apical prostate cancer lesions with irreversible electroporation (IRE)	Retrospective analysis of prospective cohort assessing safety, oncological, and quality-of-life outcomes of focal	https://link.springer.com/article/10.1007/s00345-020-03275-z	2020

			IRE for apical prostate cancer lesions.		
17.	Prospective study	Oncological and Quality-of-life Outcomes Following Focal Irreversible Electroporation as Primary Treatment for Localised Prostate Cancer: A Biopsy-monitored Prospective Cohort	Prospective study evaluating the oncological and quality-of-life outcomes following focal IRE as the primary treatment for localized prostate cancer.	https://www.sciencedirect.com/science/article/abs/pii/S2588931119300574	2020
18.	Retrospective study	Prostate cancer treated with irreversible electroporation: MRI-based volumetric analysis and oncological outcome	Retrospective study evaluating multiparametric MRI-based volumetric parameters and oncological outcomes to assess treatment efficacy and recurrence rates over a follow-up period.	https://www.sciencedirect.com/science/article/abs/pii/S0730725X18306465	2019
19.	Prospective phase II study	Image-guided Irreversible Electroporation of Localized Prostate Cancer: Functional and Oncologic Outcomes **EA4/052/13**	Prospective phase II study evaluates the urogenital toxicity and oncological outcomes of MRI–transrectal ultrasound fusion-guided IRE for the focal treatment of localized prostate cancer.	https://pubs.rsna.org/doi/10.1148/radiol.2019181987	2019
20.	Retrospective study	Prostate cancer treatment with Irreversible Electroporation (IRE): Safety, efficacy and clinical experience in 471 treatments	Retrospective study evaluating safety, efficacy, and clinical outcomes over a follow-up period of up to six years.	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0215093	2019

21.	Stage IIa, prospective development study	Nanoknife Electroporation Ablation Trial: A Prospective Development Study Investigating Focal Irreversible Electroporation for Localized Prostate Cancer **ClinicalTrials.gov Identifier: NCT01726894**	The NEAT study investigates the safety, side effects, and early oncological control of focal IRE in patients with localized prostate cancer .	https://www.auajournals.org/doi/10.1016/j.juro.2016.09.091	2017
22.	Retrospective study	Feasibility and safety of focal irreversible electroporation as salvage treatment for localized radio-recurrent prostate cancer	Retrospective study evaluating the feasibility, safety, and short-term outcomes of focal IRE as a salvage treatment for localized radio-recurrent prostate cancer.	https://bjui-journals.onlinelibrary.wiley.com/doi/full/10.1111/bju.13991	2017
23.	Prospective phase I-II study	Histopathological Outcomes after Irreversible Electroporation for Prostate Cancer: Results of an Ablate and Resect Study **ClinicalTrials.gov Identifier: NCT01790451**	Phase I-II prospective study evaluating the histopathological outcomes of IRE for prostate cancer by performing IRE on patients prior to their scheduled radical prostatectomy.	https://www.auajournals.org/doi/10.1016/j.juro.2016.02.2977	2016
24.	Pilot study	Pilot Study to Assess Safety and Clinical Outcomes of Irreversible Electroporation for Partial Gland Ablation in Men with Prostate Cancer	Pilot study assessing safety, complications, and intermediate-term functional outcomes of partial prostate gland ablation using irreversible electroporation in men	https://www.auajournals.org/doi/10.1016/j.juro.2016.02.2986	2016

			with localized prostate cancer.		
25.	Prospective phase I-II study	Quality of Life and Safety Outcomes Following Irreversible Electroporation Treatment for Prostate Cancer: Results from a Phase I-Ii Study **NCT001790451**	Phase I-II prospective multi-center clinical trial evaluating the safety, quality of life, and functional outcomes of IRE as a treatment for prostate cancer.	https://www.hilarispublisher.com/open-access/quality-of-life-and-safety-outcomes-following-irreversible-electroporation-treatment-for-prostate-cancer-results-from-a-phase-iiistudy-1948-5956-1000369.pdf	2015
26.	Retrospective study	Initial assessment of safety and clinical feasibility of irreversible electroporation in the focal treatment of prostate cancer	Retrospective study evaluating the safety and clinical feasibility of IRE as a focal treatment for localized prostate cancer.	https://www.nature.com/articles/pcan201433	2014

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

**** If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).*

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

	Type of study design*	**Title of journal article or research project** (including any trial identifier or study lead if relevant)	**Short description of research** (max 50 words)**	**Website link to journal article or research** (if available)	**Date of publication*****
1.	Randomised Control study	A randomised controlled trial of Partial prostate Ablation versus Radical Treatment in intermediate-risk, unilateral clinically localised prostate cancer	The PART study will directly compare Partial Ablation with Radical Treatments for intermediate risk prostate cancer on one side of the prostate.	https://fundingawards.nihr.ac.uk/award/17/150/01	2026
2.	Randomised Control Trial	Prostate Cancer IRE Study (PRIS): A Randomized Controlled Trial Comparing Focal Therapy to Radical Treatment in Localized Prostate Cancer	IRE PRIS study involves two parallel randomized controlled trials comparing IRE with (1) robot-assisted radical prostatectomy (RARP) or (2) radiotherapy in men with newly diagnosed intermediate-risk prostate cancer	https://pubmed.ncbi.nlm.nih.gov/37091033/	
3.	Prospective, non-randomised, pivotal trial	A Description and Safety Overview of Irreversible Electroporation for Prostate Tissue Ablation in Intermediate-Risk Prostate Cancer Patients: Preliminary Results from the PRESERVE Trial	This study aims to evaluate the safety and effectiveness of the NanoKnife System to ablate prostate tissue in patients with intermediate-risk prostate cancer (PCa).	https://www.mdpi.com/2072-6694/16/12/2178	2025

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*
***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*
**** If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).*