Introduction

Profound Medical Inc. is a legal manufacturer of Transurethral Ultrasound Ablation System (TULSA-PRO®) medical devices. This document provides an overview summary of safety and clinical performance (SSCP) for TULSA-PRO® system, per European Union's (MDR) Regulation (EU) 2017/745 for class III devices.
The Summary of Safety and Clinical Performance is intended to provide public access to an updated summary of the main aspects of the device's safety and clinical performance.
The SSCP is not intended to replace the Instructions for Use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients. TULSA-PRO® is intended to be used in Hospitals and Clinics. The following information is intended for healthcare professionals.

Manufacturer's reference number for SSCP is GCP-10374

1. Device identification and general information

1.1. Device trade name

TULSA-PRO®

1.2. Manufacturer

Profound Medical Inc. 2400 Skymark Avenue, Unit 6
Mississauga, Ontario, Canada L4W 5K5
Tel.: +1 647 476-1350
Fax: +1 647 847-3739
Manufacturer's single registration number (SRN)-CA-MF-000028761

1.3. Basic UDI-DI

7540281010008Y

1.4. Medical device nomenclature description

EMDN Code: Z12160303 Prostate Thermotherapy Instruments - Equipment for Ultrasonic oncology therapy

1.5. Class of device

Class III

1.6. Year when the first certificate (CE) was issued covering device

2016

1.7. Authorized representative

MDSS GmbH
Schiffgraben 41, 30175 Hannover, Germany
Tel.: +49 511 6262 8630
Fax: +49 511 6262 8633
www.mdss.com
SRN: DE-AR-000005430

1.8. NB's name and single identification number

British Standards Institution (No. 2797)

2. Intended use of the device

2.1. Intended purpose

The TULSA-PRO® System is intended for transurethral ultrasound ablation (TULSA) of prostate tissue.

2.2. Indication(s) and target population(s)

The TULSA-PRO® is indicated for thermal ablation of prescribed prostate tissue, benign and malignant, using transurethral ultrasound ablation (TULSA) with in-bore-real time MRI treatment, planning, monitoring, visualization, thermal dosimetry, and active temperature feedback control of thermal treatment. The system is intended for planning the treatment, monitoring the delivery of thermal therapy, controlling the shape of the generated thermal lesion, and assessing the extent of coagulation post treatment, all under MRI visualization. The TULSA-PRO® software provides MRI-based planning guidance for positioning the UA, contouring the prostate, and surrounding important anatomy, and controlling the delivery of the thermal treatment. It also provides real-time spatial temperature analysis of selected MRI images. TULSA-PRO® intended target population is men with prostate disease.

2.3. Contraindications and/or limitations

MRI Eligibility.
Patients receiving TULSA therapy with the TULSA-PRO system must be eligible for magnetic resonance imaging and must be screened by an MRI professional (technologist or radiologist) prior to entering the MRI suite for treatment. Some contraindications to MRI include (but are not limited to):

- Patients with implants that are electrical or metallic (such as pacemaker, aneurism clip, or cochlear implant)
- Metal fragments or shrapnel in the body (such as from previous metal-working experience or shrapnel)

Anesthesia:
Patients receiving therapy must be eligible for general anesthetic. Eligibility must be assessed by an anesthesiologist prior to treatment

Prostate Gland Size and Tissue.
As a guideline for a single treatment with the TULSA-PRO® System:

- If treating of a whole prostate gland, the prostate volume should be no greater than 90 cc. Men with very large prostates should not be excluded if the goal of TULSA treatment is partial gland ablation with a target ablation volume no greater than 90 cc
- the prostate gland size should be no greater than 5 cm long (cranial/caudal or superior/inferior) and 6 cm in axial diameter (left/right and anterior/posterior). The maximum extent of thermal ablation is 3 cm in radial distance from the UA center. Prostate gland tissue must not have cysts or calcifications greater than 1 cm; less than 1 cm may be acceptable provided they are not located near the periphery of the gland where temperature monitoring may occur.

Prostate Tumors

- Patients with prostate tumors that extend beyond the prostate capsule, seminal vesicle invasion, or metastases are not candidates for therapy. Disease diagnosis and risk stratification are the responsibility of prescribing physician

Special conditions that are also contraindications for TULSA therapy:

- Patients interested in future fertility
- Active urogenital infection
- Urinary tract or rectal fistula
- Urethral stenosis; making it difficult to insert the Ultrasound Applicator (UA)
- Anal or rectal fibrosis or stenosis; making it difficult to insert the endorectal cooling device (ECD)
- Presence of implants in or adjacent to the prostate that would interfere with the ultrasound beam path (such as radioactive seed implants, artificial sphincter, penile prosthesis, or intraprostatic implant)

3. Device description

3.1. Description of the device and material/substances in contact with patient tissues

The TULSA-PRO system combines real-time Magnetic Resonance (MR) imaging and MR thermometry with transurethral directional ultrasound and feedback process control software to deliver precise thermal ablation of physician prescribed prostate tissue. The system consists of both hardware and software components.

The transurethral ultrasound ablation (TULSA) treatment is delivered completely within the MR bore. A real-time MRI interface is used by feedback features of the TULSA-PRO system: real-time MRI prostate temperature measurements are processed by TULSA-PRO software which communicates with TULSA-PRO hardware, thereby controlling frequency, power, and rotation rate of ultrasound to ablate physician prescribed prostate tissue with a high degree of precision.

The physician inserts two catheters, one transurethral and another transrectal, into the patient before he is moved into the MR bore. The transurethral catheter consists of an Ultrasound Applicator (UA) which delivers energy from within the prostate tissue, heating it to thermal coagulation. The transrectal catheter is an Endorectal Cooling Device (ECD) which does not emit any energy and cools the rectal wall adjacent to the prostate. Both catheters have fluid flowing inside throughout the treatment to thermally protect the urethra and rectum, to minimize the potential of any thermal damage to either the urinary or rectal pathways.

The physician uses the TULSA-PRO console to robotically position the UA in the prostate and plan the treatment by contouring the prescribed tissue on real-time high-resolution cross-sectional MR images of the prostate. These features provide the physician with the ability and the control to customize the treatment plan to minimize thermal impact to critical structures surrounding the prostate including the external urethral sphincter, rectum, and neurovascular bundles.

The treatment begins based upon the physician’s instructions by enabling the software to start thermal ablation. The TULSA-PRO feedback process control software reads real-time MR thermometry measurements and adjusts automatically and dynamically the frequency, power and rotation rate of ultrasound provided by each UA transducer, to deliver precise ablation of the prescribed prostate tissue. The software controls automated, continuous and robotic rotation of the transurethral UA by 360 degrees in sync with the process-controlled delivery of thermal heating to all the required regions of the prostate. After the ablation process, the two catheters are removed from the patients' natural orifices.

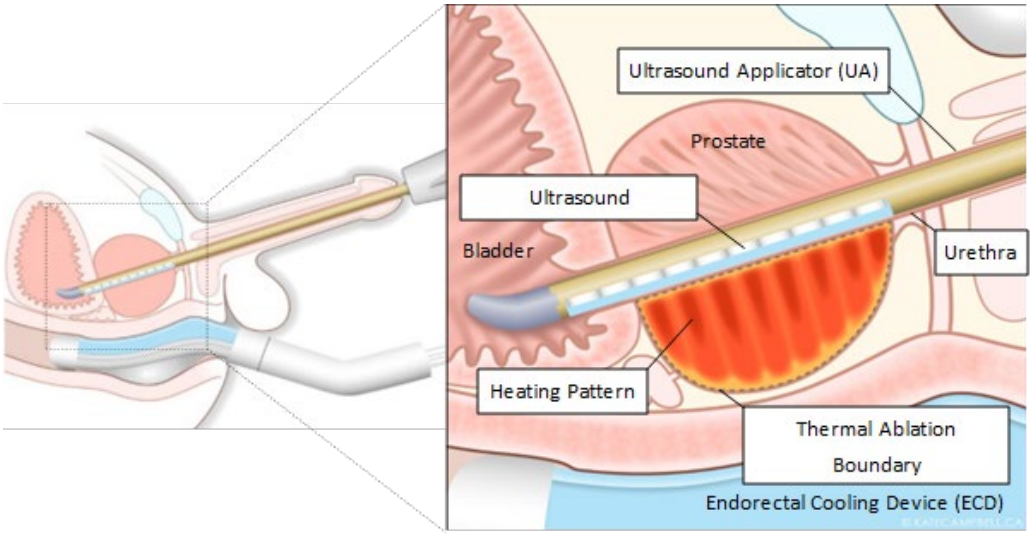


Figure 1. Conceptual diagram of the TULSA-PRO in patient.

System Components

- The TULSA-PRO system consists of:
- capital equipment
- Single-use disposable devices.

Capital equipment Capital Equipment is set up at the MRI suite as per Figure 2 below.

The equipment consists of the following components:

- Treatment Delivery Console (TDC) – custom software and user interface

- System Cart – transportable equipment cart with:
  - System Electronics – power and control signals for TULSA-PRO system
  - Fluid Circuit – cooling fluid circulation system

- Positioning System (PS) – device support, linear and rotational positioning
- PS Interface Box (PSIB) – motion control electronics and user interface

- Filter Box – shielded connection enclosure for all signals passed into MRI suite
- Magnet Kit (not shown in picture) –patient base plate and leg supports, with straps and clips (some kits may include a coil holder, if required).

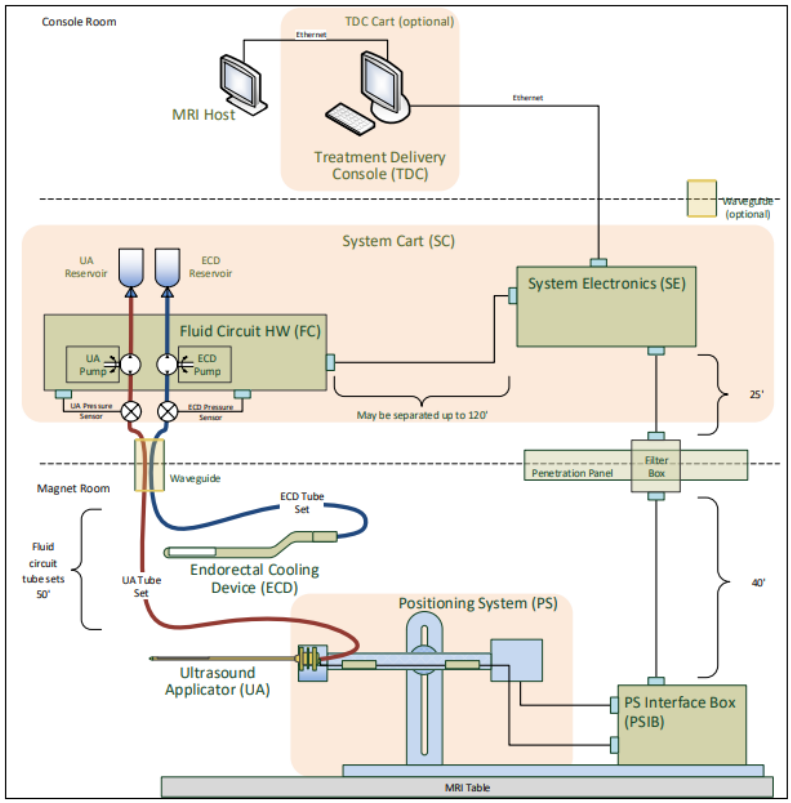


Figure 2. Diagram of the TULSA-PRO complete system. Dotted line represents the wall of the magnet room.

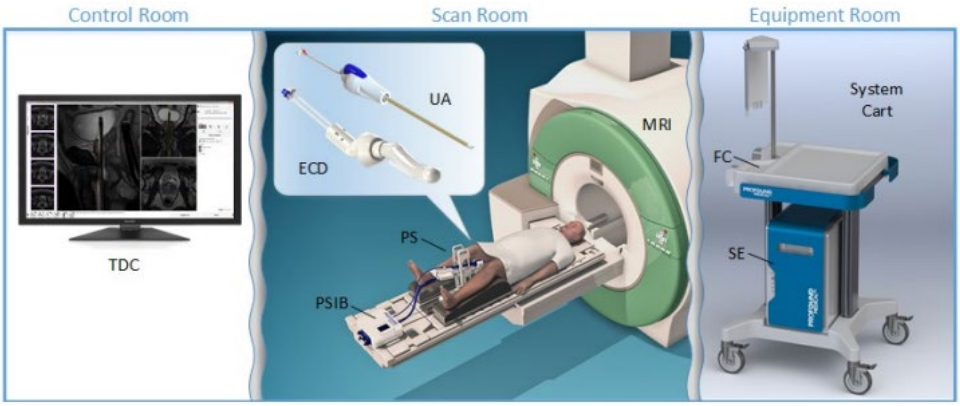


Figure 3. TULSA-PRO System Components.

Treatment Delivery Console (TDC) Software provides the main user interface for the TULSA-PRO® System. The software controls:

- Setting up the patient treatment file
- Transferring MR images from the MR scanner console
- Precise positioning of the UA in the prostate

- Treatment planning and definition of control boundary
- Accurate delivery of ultrasound to the prostate with the aid of real-time temperature feedback from the MR scanner.
- The software displays continuous information, such as intraprostatic temperatures and device parameters, during the treatment. The TDC uses feedback control algorithm to produce volumes of thermal coagulation that conforms to predefined 3D prostate geometries by using temperature and spatial anatomical measurements to modulate device rotation rate, ultrasound power, and operational frequency. New temperature and spatial anatomical measurements are received from the MRI in real-time every 5 to 7 seconds.
- The software is installed on a personal computer and a monitor, keyboard, and mouse are provided for display and interaction. The TDC is intended to be used at the MRI console with the Operator seated. The Operator must check the display during treatment delivery since the user interface displays information essential for safe operation of the TULSA-PRO® System.

3.2. Previous generation(s) or variants and description of the differences

The TULSA-PRO system has undergone hardware updates over time. Different versions of the capital equipment components were produced). The key updates include redesigned versions of the following components: the Filter Box (FB), the Positioning System (PS), and the Positioning System Interface Box (PSIB) and Ultrasound Applicator (UA). Associated cables for the UA and PS were also updated accordingly. These hardware improvements do not affect the essential performance, intended use of the system or the Basic UDI-DI of the TULSA-PRO system..

3.3. Description of any accessories which are intended to be used in combination with the device:

The TULSA-PRO system consists of several components, as described in section 3.1, that are intended to be used in combination as one system. These components are included in the CE marking of the TULSA-PRO System.

3.4. Description of other device intended to be used in combination with the device

The TULSA-PRO® system is intended to connect to and deliver treatment within a third-party MRI system. The connection to the MRI system happens through software, to the MRI console to receive real-time images, and through hardware, to the MRI table and shielded filter panel. The system is designed and verified for compatibility with multiple MRI models manufactured by Siemens, Philips, and GE. When used together with the MRI scanners, the TULSA-PRO® system is in conformity with the general safety and performance requirements.

4. Risks and warnings

4.1. Residual risks and undesirable effects

The residual risks of TULSA-PRO treatment are identified and documented in the risk management report. The listed hazards below are those remaining after risk control measures have been taken. These risks are mitigated by compliance of the system Operator with recommended practices in the user manual. The Operator can keep the risks low by following the Instructions for Use and observing Cautions as outlined in the IFU and the enclosed documents. All Residual risks are disclosed in the documentation going with the device.

- GI complications (e.g., diarrhea, bloating, straining, rectal pain)
- Damage to urethra, urethral stricture, blockage, retention, obstruction
- Urinary incontinence
- Damage to pelvic bone or nerves adjacent to bone
- Treatment of unintended tissue
- Heating muscle tissue outside of prostate
- Urethral damage, pain, or bleeding
- Pain, bruising, pressure sores, deep vein thrombosis
- Infection(urinary tract, orchitis, epididymitis)
- Thermal damage to neurovascular bundle, erectile dysfunction

The following list is a summary of TACT trial adverse events attributable to TULSA-PRO device.

ADVERSE EVENT (AE)	SUBSET OF AE ATTRIBUTABLE TO TULSA-PRO # SUBJECTS (%) (N=115)
Total	101 (87.8 %)
Erectile dysfunction	49 (42.6 %)
Haematuria	42 (36.5 %)
Urinary tract infection	32 (27.8 %)
Dysuria	21 (18.3 %)
Urinary incontinence	26 (22.6 %)
Pain/discomfort (pelvic/genital/treatment area)	25 (21.7 %)
Oedema (testicular, scrotal, penile)	24 (20.9 %)
Urinary urgency	25 (21.7 %)
Catheter site pain/inflammation	7 (6.1 %)
Pain/discomfort (abdominal/anorectal)	14 (12.2 %)

Urinary frequency	16 (13.9 %)
Bladder spasm	12 (10.4 %)
Ejaculation disorder	14 (12.2 %)
Non-descriptive LUTS	10 (8.7 %)
Urinary retention	10 (8.7 %)
Urethral bleeding	13 (11.3 %)
Pain/discomfort (hip/back)	9 (7.8 %)
Urethral discharge	11 (9.6 %)
Weak urinary stream	11 (9.6 %)
Pain/discomfort (bladder/urinary tract)	9 (7.8 %)
Fatigue	3 (2.6 %)
Nausea	2 (1.7 %)
Epididymitis	7 (6.1 %)
Headache	2 (1.7 %)
Debris in urine	5 (4.3 %)
Orchitis	2 (1.7 %)
Constipation	2 (1.7 %)
Fever	3 (2.6 %)
Nocturia	3 (2.6 %)
Urethral stenosis	3 (2.6 %)
Calculus urinary	1 (0.9 %)
Hydronephrosis	1 (0.9 %)
Urinoma	1 (0.9 %)
Deep vein thrombosis	1 (0.9 %)

4.2. Warnings and precautions

See Appendix A.

4.3. Safety, including a summary of field safety corrective action (FSCA including FSN)

There is no FSCA for the TULSA-PRO®.

5. Summary of clinical evaluation and post-market clinical follow-up (PMCF)

5.1. Summary of clinical data related to equivalent device

Currently, there is no device in the market that is equivalent to TULSA-PRO® by design.

5.2. Summary of clinical evidence for CE-marking

Data from a pre-market clinical investigation, the 30 patient Phase I clinical trial were available from manufacturer-held databases supplemented by peer-reviewed publications.
Phase I study prospectively assessed the safety and performance of TULSA-PRO® according to the proposed intended use. The first one-year primary safety and ablation efficacy results of the Phase I clinical trial formed the basis for issuance of CE Marking.
Five-year outcomes of TULSA-PRO as primary treatment for prostate ablation in adult men included device safety, performance (accuracy and precision of thermal ablation), efficacy (PSA, prostate biopsy), and impact on quality of life.

5.3. Overview and appraisal of clinical data

This section summarizes the aggregated clinical data available from clinical investigations, manufacturer-held sources, and scientific literature. Sources include feasibility studies, pivotal clinical investigations, PMCF studies, and other use data as described in previous sections.

The TULSA-PRO systems used to collect clinical data in the pivotal study (TACT) and the Phase I study were developed and manufactured in accordance with requirements of MDD COUNCIL DIRECTIVE 93/42/EEC, Annex I. These prospective studies were conducted in accordance with MDD COUNCIL DIRECTIVE 93/42/EEC, Annex X, and ISO 14155:2011 international standard. These clinical investigations conducted by the manufacturer in the United States comply with 21 CFR parts 50, 56 and 812. Clinical investigations conducted by the manufacturer outside the United States are conducted in accordance with Good Clinical Practice (GCP) as described in 21 CFR 8.12.28(a)(1).

The largest cohort in which TULSA-PRO was evaluated comprises the prospective TACT pivotal study, designed to assess the safety and performance of the device, according to the proposed intended use. The 12-month outcomes of the TACT study represent the primary set of clinical data used to evaluate safety, efficacy, and the majority of the claims of the device and are supported by the manufacturer-held long-term follow-up [Klotz *et al* 2021]. The TACT study examined the outcomes of TULSA-PRO prostate tissue ablation in patients with localized, organ-confined prostate cancer. Primary endpoints assessed 12 months after treatment with the TULSA-PRO device include safety (frequency and severity of adverse events), and efficacy (proportion of patients achieving a PSA nadir less than 25% of the pre-treatment baseline value). Secondary endpoints assessed at 12 months included PSA stability; reduction in prostate volume; proportion of patients with negative and clinically insignificant biopsy; changes in patient reported quality of life including erectile, urinary and bowel function; and evaluation of multiparametric prostate MRI.

Earlier, TULSA-PRO was also evaluated in a pre-market Phase I study designed to assess the safety and performance of the device, according to the proposed intended use. 12-month data from the Phase I study formed the basis for CE Marking. Longer-term data from the Phase I study examined the outcomes of TULSA-PRO as primary treatment for prostate ablation in adult men, assessing to 5 years the device safety, performance (accuracy and precision of thermal ablation), PSA, prostate biopsy and impact on quality of life [Hatiboglu *et al* 2023]. The 12-month outcomes of the Phase I study represent a supporting set of clinical data used to evaluate safety, performance and claims of the device. Three- and five-year following from the Phase I study provides additional supporting data on long-term safety. Manufacturer-held data is further supported by six publications identified in the literature search, which report the 12-month safety and performance outcomes [Chin *et al* 2016], technical performance and 12-month radiologic outcomes [Bonekamp *et al* 2018], 3- and 5-year follow-up [Chin *et al* 2018; Nair *et al* 2020; Hatiboglu et al 2023]. A subgroup analysis of men treated in the Phase I study and who had LUTS at baseline was performed to assess whether TULSA could incidentally relieve urinary symptoms [Elterman 2021].

Prototype research versions of the TULSA-PRO were used in two pre-market Phase 0 basic feasibility clinical academic studies [Chopra *et al* 2012, Ramsay *et al* 2017]. Both studies used “treat-and-resect” protocols, where patients underwent a radical prostatectomy immediately after the MRI-guided transurethral ultrasound treatment. These studies demonstrate the accuracy and precision of thermal ablation both on MR thermometry images acquired during treatment delivery and on whole-mount prostate histology correlated to the MR images. The timing of the radical prostatectomy, however, precludes assessment of device related adverse events, as well as other clinical outcomes such as PSA and quality of life. Therefore, the Phase 0 studies are included in the evaluation as supporting evidence of device performance and thermal cell kill.

The TULSA-PRO system is being further studied in an investigator-initiated clinical trial (NCT03350529) by independent researchers at the University of Turku in Finland, for which partial data is available. This study has four different arms, each with endpoints of treatment accuracy, efficacy, safety, and quality of life, and includes primary PCa, radiorecurrent PCa, locally advanced PCa and BPH populations. Clinical post-market surveillance data related to the ongoing investigator-initiated clinical study, as well as commercial TULSA-PRO treatments performed in Europe under CE Mark, are summarized based on the Post Market Surveillance report in Section 5.5.1.4. Other investigator-initiated studies and sponsored studies (‘CARE’ registry and ‘CAPTAIN’ randomized controlled trial) are indicated in Table 4 and have yet to report results.

The clinical studies and sources of manufacturer-held data listed above were evaluated for suitability and data contribution according to the criteria outlined in Table 1. Given the limited number of studies, weighting of the appraisal criteria was not necessary to determine the relative contribution of each study to the evaluation of the safety and performance of TULSA-PRO. A tabulation of the clinical data is provided in Table 2, outlining the data suitability and contribution for the purposes of evaluating safety and performance of the TULSA-PRO. The TACT pivotal study represents the primary clinical dataset used to assess safety and efficacy of TULSA. The other clinical data are included in the evaluation and used as primary or secondary data sources as appropriate.

Criteria	Description	Grading System
Appraisal Criteria for Suitability of Clinical Data		
Appropriate device	Were the data generated from the device in question?	D1 Actual device D2 Other device

Appropriate device application	Was the device used for the same intended use?	A1 Same use A2 Minor deviation A3 Major deviation
Appropriate patient group	Were the data generated from a patient group that is representative of the intended treatment population and clinical condition?	P1 Applicable P2 Limited P3 Different population
Acceptable report/data collation	Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?	R1 High quality R2 Minor deficiencies R3 Insufficient information
Appraisal Criteria for Data Contribution of Clinical Data		
Data source type	Was the design of the study appropriate?	T1 Yes T2 No
Outcome measures	Do the outcome measures reported reflect the intended performance of the device?	O1 Yes O2 No
Follow-up	Is the duration of follow-up long enough to assess treatment effects and identify complications?	F1 Yes F2 No
Statistical significance	Has the statistical analysis of the data been provided and is it appropriate?	S1 Yes S2 No
Clinical significance	Was the magnitude of the treatment effect observed clinically significant?	C1 Yes C2 No
Post-market clinical follow-up	Does the study contain post-marketing clinical follow-up data?	M1 Yes M2 No

Table 1. Appraisal criteria used to evaluate suitability and data contribution of the clinical investigations data.

Phase/Study	Data Suitability	Data Contribution	Device Safety	Device Performance	Data Supporting Claims in claim * Claims 6 & 7 are by design (Section 3.3)
Pivotal TULSA-PRO Ablation Clinical Trial (TACT) (Klotz 2021, Eggener 2024, Manufacturer-held data)	D1 Actual device A1 Same use P1 Applicable R1 High quality	T1 Yes O1 Yes F1 Yes S1 Yes C1 Yes M1 Yes	Yes – assesses acute and long-term safety and patient quality of life; 5 year outcomes available.	Yes – assesses performance based on imaging	1. Primary dataset[1] 2. Primary dataset 3. Primary dataset 4. Supportive dataset 5. Primary dataset 8. Primary dataset 9. Primary dataset
Phase I clinical [Chin *et al* 2016, Nair 2020, Hatiboglu *et al* 2023, manufacturer-held data]	D1 Actual device A1 Same use P1 Applicable R1 High quality	T1 Yes O1 Yes F1 Yes S1 Yes C1 Yes M1 Yes	Yes – assesses acute and long-term safety and patient quality of life; 5 year outcomes available.	Yes – assesses performance based on imaging	1. Supportive dataset[1] 2. Supportive dataset 3. Supportive dataset 4. Primary dataset 5. Supportive dataset

Phase 0 clinical [Ramsay *et al* 2017]	D2 Equivalent device A2 Minor deviation P1 Applicable R2 Minor deficiencies	T1 Yes O1 Yes F2 No S2 No C1 Yes M2 No	No – timing of radical prostatectomy precludes assessment of device safety	Yes – assesses performance based on imaging and whole-mount prostate histology	1. Primary dataset[1] 4. Supportive dataset
Phase 0 clinical [Chopra *et al* 2012]	D2 Equivalent device A2 Minor deviation P1 Applicable R1 High quality	T1 Yes O1 Yes F2 No S1 Yes C1 Yes M2 No	No – timing of radical prostatectomy precludes assessment of device safety	Yes – assesses performance based on imaging and whole-mount prostate histology	1. Primary dataset[1] 4. Supportive dataset
Articles included in systematic review of TULSA	D1 Actual device A1 Same use P1 Applicable R1 High quality	T1 Yes O1 Yes F1 Yes S1 Yes C1 Yes M1 Yes	Yes – assesses acute and medium-term safety and quality of life.	Yes – assesses performance based on PSA decline and clinically-directed need for additional cancer treatment.	1. Supportive dataset 2. Supportive dataset 3. Supportive dataset 5. Supportive dataset 10. Supportive dataset 11. Supportive dataset

Table 2. Tabulation of the clinical data used to evaluate the safety and performance of the TULSA-PRO.
[1] The two Phase 0 studies are included in the primary dataset to support claims of prostate ablation through thermal coagulation providing cell kill indiscriminate of prostate tissue type (normal and cancerous tissues), owing to the production of gold-standard whole-mount histopathology sections in these studies.

5.3.1. Summary of TACT pivotal trial

MRI-guided TULSA was evaluated in a single-arm, multi-center, prospective pivotal study sponsored by PMI to determine the safety and efficacy of the TULSA-PRO device in patients with localized prostate cancer [Klotz et al 2021]. Treatment intent was whole-gland ablation with sparing of the urethra and urinary sphincter. Patient enrollment was completed February 8, 2018 with 115 patients at 13 trial sites across the United States, Canada and Europe:

- United States – Johns Hopkins Medicine, PI: Christian Pavlovich
- United States – Vanderbilt University Medical Centre, PI: David Penson
- United States – Indiana University, PI: Michael Koch
- United States – University of California Los Angeles, PI: Steven Raman
- United States – University of Chicago, PI: Aytekin Oto
- United States – University of Southwestern Medical Center, PI: Yair Lotan
- United States – William Beaumont Hospital, PI: James Relle
- Canada – Sunnybrook Health Sciences Centre, PI: Laurence Klotz
- Canada – London Health Sciences Centre, PI: Joseph Chin
- Germany – University of Heidelberg, PI: Gencay Hatiboglu
- Germany – University Hospital of Cologne, PI: Thorsten Persigehl
- Netherlands – Radboud University Medical Center, PI: Jurgen J Futterer
- Spain – ResoFus Alomar together with Hospital Universitari De Bellvitge, PI: Juan Ignacio Pascual

A total of 115 patients underwent whole-gland prostate ablation with TULSA-PRO as primary treatment for biopsy-proven low/intermediate risk prostate cancer: clinical stage ≤ T2b; PSA ≤ 15 ng/ml; Gleason score ≤ 3+4; age 45-80 years. Of the 115 patients enrolled in the study, 77 (67.0%) had NCCN intermediate-risk disease, 72 (62.6%) had Grade Group 2 (GG2, Gleason Score 3+4) or worse cancer, 26 (22.6%) had high-volume GG1 disease (Gleason Score 3+3, max core involvement ≥50% or >2 positive cores), and 17 (14.8%) had low-volume GG1 disease (Gleason Score 3+3, max core involvement <50% or ≤2 positive cores).

Under general anesthesia and supra-pubic catheter (SPC) drainage, the transurethral device was inserted without difficulty and positioned in the prostatic urethra using MRI guidance. Treatment planning was performed under MRI prostate visualization. Ultrasound treatment was delivered to the prescribed prostate volume identified during the treatment planning stage under continuous real-time MRI thermometry feedback control. Primary endpoints were safety (frequency and severity of adverse events) and efficacy (proportion of patients achieving a PSA nadir ≤ 25% of the pre-treatment baseline value, with a pre-established performance goal for the success proportion of 50% of patients). Clinical follow-up included serial PSA, uroflowmetry, QoL questionnaires (IPSS, IIEF, EPIC), and 12-month prostate biopsy and MRI. TACT data included in this report captures the 12-month follow-up visit of all patients, with locked database copy 02-Apr-2019 [GCP-10256; Klotz et al 2021]. The present report also includes manufacturer-held post-market follow-up to 5 years.

Adverse Events (AE) were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) developed by the NCI and were standardized to medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). To 12 months, there was no rectal injury or fistula, and no severe urinary incontinence or erectile dysfunction. There was no attributable Grade 4 or higher AE. Attributable Grade 3 AE were present in 7.8% of patients, all resolved by the 12-month follow-up. The majority of attributable events were moderate Grade 2, related to the genitourinary system which also resolved by 12 months.

Median (IQR) ultrasound treatment time was 51 (39-66) min and prostate volume 40 (32–50) cc. Spatial accuracy and precision of thermal ablation was 0.1 ± 1.4 mm, with the conformal NPV confirmed on CE-MRI after treatment. The primary endpoint of PSA nadir ≤ 25% of pre-treatment baseline value was achieved in 95.7% (110/115) patients. The median PSA reduction was 95% to a 5-year nadir of 0.27 ng/ml, stable from 0.53 ng/ml at one year to 0.63 ng/ml at 5 years. IPSS and EPIC urinary incontinence scores returned to pre-treatment values by 3 months, remaining stable to 12 months. IIEF Erectile Function (EF) scores decreased at 1 month, with gradual improvement towards pre-treatment values by 12 months. At 12 months, the median perfused prostate volume of patients in TACT decreased 91.4% from 37.3 cc to 2.8 cc, based on per-protocol assessment from a central radiology core lab (n=106 patients with readable images prior to and after TULSA).

Of the 115 patients enrolled in the study, 4 (3.5%) did not undergo follow-up biopsy, in all cases due to patient refusal. Among 68 men with pre-treatment intermediate risk GG2 or worse disease, 54 (79.4%) were free of GG2 or worse disease on one-year biopsy. Among 94 men with pre-treatment GG2 or high-volume GG1 (Gleason Score 3+3, max core involvement ≥50% or >2 positive cores) or worse disease, 72 (76.6%) were free of GG2 or high-volume GG1 or worse disease on follow-up biopsy. Of 111 men with one-year biopsy data, 72 (64.9%) had a complete histological response with no evidence of any cancer, and 16 (14.4%) had low-volume GG1 disease (≤2 positive cores, <50% max core involvement). Among the 17 men with pre-treatment low-volume GG1 disease, 13 (76.5%) had a complete histological response with no evidence of any cancer.

The TACT pivotal study of MRI-guided TULSA in men with localized prostate cancer met its primary endpoint of ≥ 75% PSA reduction in 96% of patients with a 92% reduction in prostate volume, and low rates of severe toxicity and residual GG2 disease. The 12-month outcomes of the TACT study demonstrate that MRI-guided TULSA is a safe

and effective treatment for the accurate and precise conformal ablation of prostate tissue. The PMI TULSA-PRO device provides accurate treatment planning, real-time thermal dosimetry and precise control of prostate ablation, with a well-tolerated side-effect profile.

The five-year follow-up visit was completed by 93 patients. Grade 3 (severe) adverse events occurred in 9 men (8%) with resolution before 1 year, and in 2 men (2%) with onset and resolution between 1-2 years: genitourinary infection, stricture, retention, urethral calculus, pain, urinoma, LUTS. No grade 4 or higher attributable adverse events have been reported to date. There was no rectal injury or fistula, and no severe urinary incontinence or erectile dysfunction. Median PSA decreased 96% to a 5-year nadir of 0.27 ng/ml, stable from 0.53 ng/ml at one year to 0.63 ng/ml at 5 years. 25 men (21.7%) underwent additional treatment for prostate cancer without complications: 10 salvage radical prostatectomy (RP); 11 radiation therapy (EBRT and brachytherapy); 1 RP and EBRT; 3 radiation therapy and ADT. Quality of life scores continued to recover to five years. The proportion of patients preserving International Index of Erectile Function-15 Q2≥2 potency increased from 75% at one year to 77% at five years. The proportion of patients preserving social continence (Expanded Prostate Cancer Index Composite, EPIC Q5; ≤1 pad/day) was 99% at one year, and 97% at five years. The proportion of patients preserving (EPIC Q5) pad-free continence was 92% at one and five years. The median (IQR) International Prostate Symptom Score decreased from 7 (3-10) at baseline to 6 (3-9) at 1 year, stable to 4.5 (3-13.5) at five years. EPIC bowel domain score was stable from median (IQR) 96 (93-100) at baseline to 98 (91-100) at five years.

5.3.2. Summary of Phase I clinical trial

MRI-guided TULSA was evaluated in a single-arm, prospective Phase I clinical study sponsored by PMI to determine the safety and device performance of the TULSA-PRO in patients with localized prostate cancer [DOC-10246, GCP-10099, Chin *et al* 2016, Bonekamp *et al* 2018, Chin *et al* 2018, Nair et al 2020a, Nair et al 2020b]. Patient enrollment spanned March 2013 to March 2014 at three trial sites: Dr. Joseph Chin at Western University (UWO), London Health Sciences Center, London ON, Canada; Dr. Heinz-Peter Schlemmer at the German Cancer Research Center (DKFZ), Heidelberg, Germany; and Dr. James Relle at William Beaumont Health System, Royal Oak MI, United States.

A total of thirty patients underwent prostate ablation with the TULSA-PRO as primary treatment for their biopsy-proven low/intermediate-risk prostate cancer: cT1c – T2a; PSA ≤ 10 ng/ml; Gleason score ≤ 3+3 (maximum 3+4 allowed in Canada only); age ≥ 65 years. Under general anesthesia and supra-pubic Catheter (SPC) drainage, the transurethral device was inserted without difficulty and positioned in the prostatic urethra using MRI guidance. Treatment planning was performed under MRI prostate visualization. To measure technical performance and precision of ablation within prostate gland, a 3 mm margin was selected from the prostate periphery, leaving approximately 10% residual prostate volume distributed around the gland periphery. Ultrasound treatment was delivered to the target identified during the treatment planning stage under continuous real-time MRI thermometry feedback control.

Primary endpoints were safety (frequency and severity of adverse events) and device performance (conformal thermal ablation on MRI thermometry and CE-MRI). Clinical follow-up included serial PSA, QoL questionnaires (IPSS, erectile function domain of the IIEF, and bowel habits domain of the UCLA-PCI-SF), 12-month prostate biopsy and MRI, and 3-year biopsy. Phase I data included in this report captures the 12-month follow-up visit of all patients dated 13-Apr-2015 [GCP-10099], updated according to subsequent publications and all manufacturer-held data to 5 years at the close of the study [IDEG130103 R015 Final Report 2022].

Adverse Events (AE) were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4. To 12 months, there were no intraoperative complications, no rectal injury or fistula, and no severe urinary incontinence. There were no Grade 4 or higher AE, and only one related or possibly related Grade 3 AE (epididymitis in 1 patient, resolved with IV-antibiotics). The majority of events were *acute* Grade 1 and 2, related to the genitourinary system. During post-market clinical follow-up beyond the 12-month visit, there have been no attributable Grade 3 or higher AE, and no serious AE.

Median (5%–95%) ultrasound treatment time was 36 (24–54) min and prostate volume 44 (30–89) cc, with targeted prostate tissue volumes of 31 (21–68) cc. Spatial accuracy and precision of thermal ablation was 0.1 ± 1.3 mm, with the conformal NPV confirmed on CE-MRI after treatment. Median PSA decreased 87% from 5.8 (2.8–8.9) ng/ml to 0.8 (0.1–3.2) ng/ml at 1 month, remaining stable at 0.8 (0.1–3.2) ng/ml to 12 months, and 0.8 (0.2–2.7) ng/ml at 3 years. IPSS and UCLA-PCI-SF bowel habits domain scores returned to pre-treatment values by 3 months, remaining stable to 12 months and 3 years. IIEF Erectile Function (EF) scores decreased at 1 month, with improvement and return to pre-treatment values by 12 months, stable to 3 years. MRI and biopsy at 12 months show diminutive prostate volumes, averaging 51% fibrosis (n=29), with an 88% reduction in viable prostate volume. Positive biopsies at 12 months demonstrate 61% reduction in total cancer length.

Of 30 patients treated, one withdrew prior to completion of the 12-month follow-up visit (refusal to complete study procedures, except for 12-month PSA). Since completion of the 12-month follow-up visit, nine additional patients have withdrawn from the study in order to seek alternative treatment for prostate cancer (6 radical prostatectomy, 2 radiotherapy, 1 focal laser ablation). Salvage radical prostatectomy was demonstrated to be feasible, with no surgical complications [Chin *et al* 2018]. Only 2 of 22 patients who underwent 3-year biopsy experienced histological upgrading with respect to their 12-month biopsy, while 4/9 patients with positive 12-month biopsy downgraded to Gleason 3+3 or negative biopsy at 3 years. Of the 30 patients treated in the Phase I study, 9 had symptomatic lower urinary tract symptoms with baseline IPSS scores of at least 12. At 12 months after TULSA, IPSS improved by 9.8 ± 7.1 (58 ± 34%) to 6.3 ± 5.0 (paired t-test p=0.0033), with at least a moderate (> 5 point) reduction experienced by 8/9 patients (89%), and a reclassification to mild symptoms (IPSS score ≤ 7) in 7/9 patients (78%). IPSS QoL improved by 2.0 ± 1.7 to 0.8 ± 1.0 (p=0.0068), with 8/9 patients (89%) reporting as “pleased” or “delighted”. Qmax increased to 21.9 ± 12.7 ml/s, but did not reach significance (p=0.13). Prostate volume measured on T2-weighted MRI (less the non-perfused cavity) decreased by 70 ± 19% to 14 ± 5 cc (p=0.001). These improvements in urinary symptoms following TULSA-PRO treatment are comparable to those obtained with standard of care treatments for benign prostate hyperplasia:

Between three and five years, one additional patient received salvage therapy. A total of three men withdrew from the study with stable PSA, and one died of unrelated cause after four years. The median (IQR) PSA at 5 years for the 16 men remaining on study was 0.6 (0.4-1.2) ng/mL. Mean (95% CI) International Prostate Symptom Score (IPSS) decreased from 9.0 (7.0-11) to 7.1 (5.0-9.1) from baseline to five years; IPSS-QOL, maximum urinary flow rate and post-void residual urine were stable or improved. The mean (95% CI) IIEF-EF domain score decreased from 9.5 (5.2-18) at 12 months to 3 (2.7-14) at 5 years, at which time the median age was 74. Maintenance of bowel function and urinary continence was 100%. Pad-free continence was maintained in all patients. There was no new attributable serious or severe adverse event from one to five years [Hatiboglu et al, 2023].

The results of the Phase I study demonstrate that MRI-guided TULSA is a safe and feasible procedure for the accurate and precise conformal ablation of prostate tissue. The PMI TULSA-PRO device provides accurate treatment planning, real-time thermal dosimetry and precise control of prostate ablation, with a well-tolerated side-effect profile.

5.3.3. Summary of manufacturer-held post-market clinical data

The summary of post-market clinical data from the TACT pivotal trial and the Phase I trial are described in Sections 5.2.2 and 5.2.3. There is no additional clinical data arising from risk management activities. However, risk management, production, and post market data are reviewed during an annual post market surveillance meeting.

The most recent post-market surveillance meeting was held on 23 October 2024. It identified that after release to market in Europe in 2016, followed by regulatory clearance in the US and Canada in 2019, the current customer base includes over 50 hospitals and clinics across EU, US, Canada, Japan, Philippines, and India increasing from 21 in 2021, and 14 in 2020. There was one reportable incident summarized in Section 5.4. No reportable field safety corrective actions, product recalls, field corrections/removals, or increases in the rate of serious incidents were identified during the review period between July 2023 and July 2024.

Customer complaints related to technical issues identified in monthly complaint review meetings to have occurred repeatedly and resulted in corrective action included: incomplete ablation attributed at least in part to an ultrasound applicator manufacturing defect affecting electrical performance (CPA-00362), procedure delays related to cable failures and communication errors (CPA-00316, CPA-00406, CPA-00418, CPA-00407, CPA-00382, CPA-00403), customer dissatisfaction related to imaging artifacts partially obscuring the prostate during treatment planning (CPA-00360), procedure delays related to overly sensitive MR thermometry processing alarms (CPA-00396), and procedure delays related to air bubbles around the ECD (CPA-00361). User feedback on the top issues were aligned with these trends in customer complaints. As summarized in the Risk Management Production and Post Market Monitoring Report (DOC-13768), technical nonconformances identified during production led to a handful of corrective actions related to understanding cosmetic markings and improved chip potting on ultrasound applicators, reducing leak failure on endorectal cooling devices, and improving reliability of motion control and communication for the positioning system and its interface box.

Detailed post-market customer feedback in the form of real-world data and user surveys was collected on two specific updates to the TULSA-PRO system: Thermal Boost, and Endorectal Cooling Device with Bubble Removal Feature. These updates were developed in response to user feedback related to the consistency of ablation at large treatment radii, and procedure delays related to air bubbles adjacent to the ECD. In the first 25 patient treatments using the Thermal Boost feature, physicians reported that the feature likely improved treatment outcomes in 22 cases (88%) and offered the same treatment in the remaining 3 cases (12%). Qualitative assessment of heating quality indicated that 92% of cases with Thermal Boost had complete ablation of the intended target volume, compared to 68% of cases in the TACT clinical trial where the feature was not available. There was no change in risk, with similar or better rates of adverse events and non-enhancing tissue outside of the prostate. In the first 30 patient treatments using the ECD with bubble removal feature, the time spent removing air bubbles was less than 30 minutes in all cases and adequate cooling was measured on MR thermometry, with no new risks related to rectal heating or gastrointestinal complications. The additional device setup time required for the bubble removal feature was deemed acceptable. Both reports concluded that there was no increased patient risk associated with these updates to the TULSA-PRO system.

To measure the clinical safety and performance of the subject TULSA-PRO system with the Thermal Boost feature, clinical performance was validated as follows. Clinical data were collected in a post-market study conducted in Europe, in compliance with relevant GCP requirements. The following endpoints were defined:

(1) Safety (primary endpoint): Rates of serious adverse events and adverse events were compared between the benchmark device (TULSA-PRO without Thermal Boost applied) deriving from pivotal study data, and the device with the Thermal Boost feature applied in a similar patient population. Clinical follow-up of at least 6-month

duration post-treatment was assessed to identify adverse events, using MedDRA for terminology and the Clavien-Dindo classification for grading. All events were captured regardless of causality.

(2) Technical performance (secondary endpoint): System performance defined by controller accuracy was evaluated with Thermal Boost enabled and compared against the requirements, for Dice Similarity Coefficient, percentage volume overshoot and percentage volume undershoot. The comparison was performed between the physician-defined ablation plan and the temperature maps measured by the software during the ablation. Technical performance objectives are the same as were evaluated for the benchmark device clearance (K191200).

A usability assessment was also performed via questionnaire administered to physicians who used the TULSA-PRO System with the Thermal Boost feature activated. The purpose of this assessment was to determine whether the system console clearly conveyed that Thermal Boost was activated and if Thermal Boost led to any “close calls” (instance of user at risk of forgetting that a certain element was enabled for Thermal Boost). Physicians were also asked to identify the expected risks of heating outside of the prostate.

The clinical performance data were collected from 71 adult male patients treated with the TULSA-PRO system with Thermal Boost applied where needed. The area of prostate requiring Thermal Boost was determined by the treating physician. Demographic information was available for 48/71 patients. All 48 patients were reported as White/Caucasian. The median (IQR) age was 71 (64-75). Adverse event data was available from 58 of the 71 patients. Adverse events reported with Thermal Boost were those reported in the pivotal TACT study for TULSA-PRO: epididymitis, urinary retention, pain/discomfort, urinary urgency, nocturia, urinary incontinence, ejaculation disorder, erectile dysfunction, urinary tract infection, and hematuria. There was no significant increase in the rate of both adverse events and severe adverse events when Thermal Boost was applied, relative to the benchmark device. There was one Grade 3(b) adverse event in the Thermal Boost population, urinary retention, which was resolved with transurethral resection of the prostate. Treatment targeting statistics were calculated for all 71 patients who were treated with Thermal Boost applied. With the Thermal Boost enabled during treatment, all technical endpoints met the established performance criteria. Usability data were gathered from treating physicians over the first 25 patients treated. Responses from the usability questionnaire indicated that identification of the feature and training material was effective and there were no new user errors or risks identified. The results from the clinical data do not indicate any new risks or any concerns about safety or performance of the modified TULSA-PRO software with Thermal Boost compared to the predicate software.

5.3.4. Summary of clinical data from other sources

In addition to the data from clinical investigations and manufacturer-held sources described above, this section summarizes data available in public databases and the scientific literature.

The identification of published results from technical or pre-clinical studies, or clinical investigations relevant to the safety and performance of the TULSA-PRO System was conducted using the PubMed and EMBASE databases. PubMed is the largest source of relevant information (both favorable and unfavorable). To ensure coverage of European studies and the most important conference papers, the search was repeated using the EMBASE database. The accuracy and integrity of the data selected from search results is assured to a reasonable degree by selecting articles and conference abstracts only from well-known, peer-reviewed scientific journals. To limit the results of the database search to publications relevant to the safety and performance of TULSA-PRO, the search was performed using keywords that identified, at minimum, all studies known to the author a priori (listed below). No limits were placed on language, article type, or publication date.

Search string for PubMed search:

((transurethral ultrasound) OR (TULSA)) AND ((MRI) OR (magnetic resonance imaging)) AND ((therapy) OR (treatment) OR (ablation) OR (coagulation)) AND (prostate)
and EMBASE search:
("transurethral ultrasound" OR "TULSA") AND ("MRI" OR "magnetic resonance imaging") AND ("therapy" OR "treatment" OR "ablation" OR "coagulation") AND "prostate"

The systematic search was performed by Luke Chung on January 9 2025. Records were filtered for relevant systematic reviews or meta-analyses, retrieving one record [Dora et al 2022]. The search strategy applied in the retrieved systematic review was as follows. Review articles, opinion pieces, case reports, technical development articles, and preclinical studies were excluded. To generate a pool of studies with longitudinal outcomes, both initial and follow-up reports were included. If multiple studies on overlapping cohorts reported identical outcomes and follow-up time, the study with the largest sample size was selected. Conference abstracts and presentations were included if the cohort, outcomes, and follow-up times were not duplicated in a published article or a repeat presentation. The records were also filtered for men treated for prostate cancer and for records with at least one clinical outcome. The PRISMA flow diagram from the systematic search is shown in Figure 4.

The published systematic review [Dora et al 2022] utilized raw exports from the database searches, which were reviewed to identify records that report at least one clinical outcome. The exports were searched for articles relating to TULSA treatment, which resulted in a total of 25 records. Technical development records (n=29) that did not report clinical outcomes were excluded. Regarding inclusion criteria, for complete longitudinal data full articles with overlapping cohorts were included to capture all follow-up data. For articles with overlapping cohorts, duplicate endpoints and follow-up duration, the record associated with the largest cohort was selected. For conference abstracts, only the latest follow-up was included unless duplicated in a full manuscript.

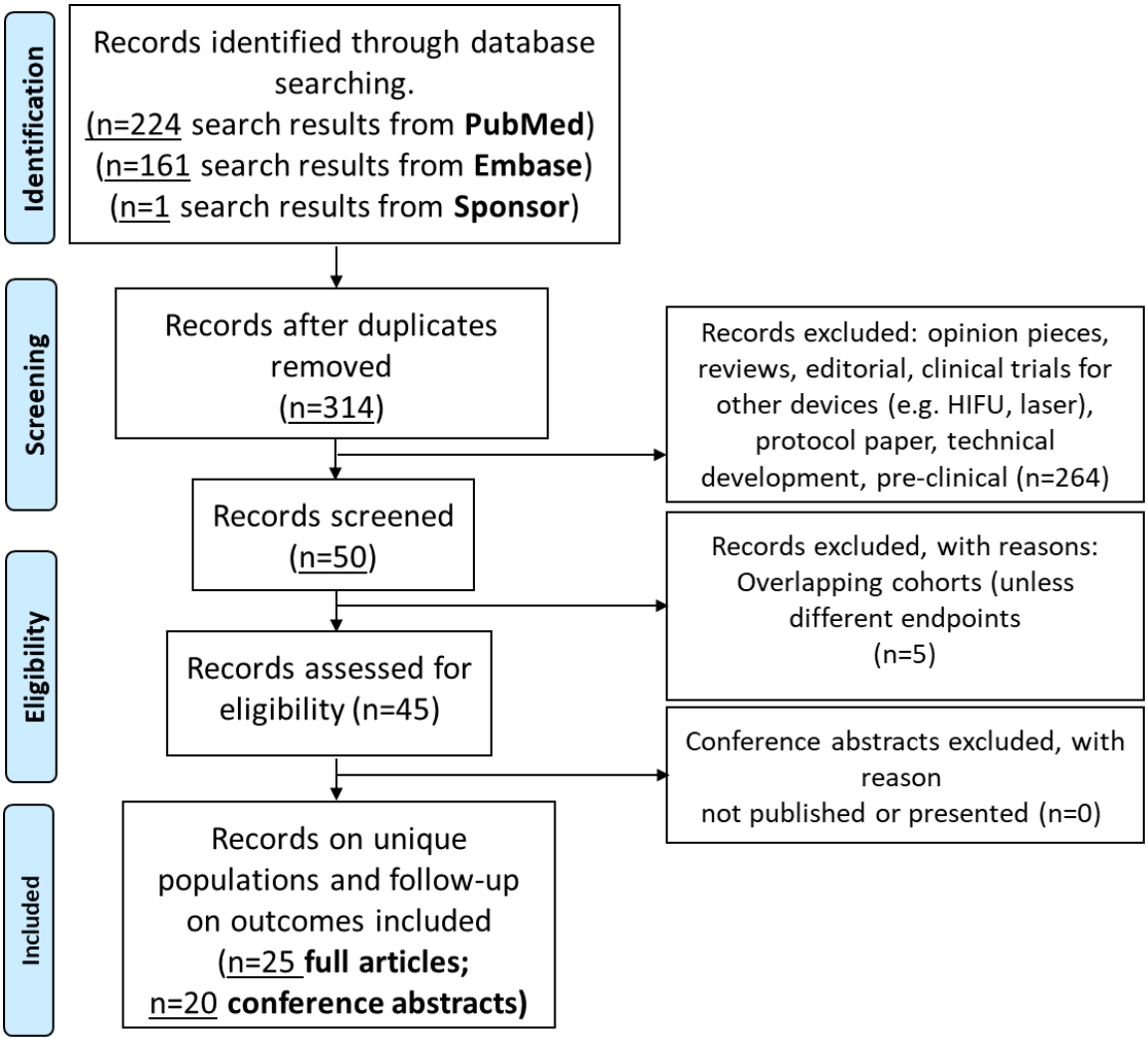


Figure 4. PRISMA flow diagram from the systematic literature search for clinical reports on TULSA. (*For full articles with overlapping cohorts, records associated with the largest cohort and all follow-ups were included, **For conference abstracts with multiple follow-ups, records corresponding to the latest follow-up were included)

From the literature search, 696 patients were treated with TULSA across 26 studies, with follow-up ranging from 6 weeks to 5 years. Populations were primary localized PCa (n=600 patients, 14 unique cohorts), recurrent PCa after radiotherapy or other treatment (n=46, 2 cohorts), benign prostatic hyperplasia (n=40, 2 cohorts), and locally advanced prostate cancer (LAPC) with patients treated palliatively (n=10, 1 cohort). There was also a subgroup of 33 patients with primary or recurrent PCa concurrent with LUTS, and the literature includes analysis of whether these patients receive incidental relief of symptoms. The LAPC cohort was comprised of men requiring surgical treatment for urinary retention and gross hematuria. Publications from the TACT and the Phase I studies are included in the clinical literature and supplemented with manufacturer-held data; the Phase 0 studies are described separately. All 26 studies reported the outcomes after a single TULSA treatment.

From Dora *et al*, efficacy, functional and safety outcomes were available for all but one cohort at median 12-16 month follow-up (IQR for 16 months: 12-22). 145 men were enrolled in studies collecting extended follow-up (2-5 years), with 3- and 5-year follow-up available for 22 and 16 men. Of the 198 men treated for primary PCa with

available data, the risk stratification was: 35% (n=69) low, 60% (n=118) intermediate, 5.6% (n=11) high-risk [Dora *et al*, 2022]. Median age in the LAPC cohort was 76.5 (range: 60-81), and in all other cohorts mean or median age was 66-71 [Dora *et al*, 2022]. At baseline, the men in the LAPC study suffered gross hematuria (9/10) and urinary retention requiring continuous catheterization (10/10) due to bladder outlet obstruction [Dora *et al*, 2022]. 33 men with primary or recurrent PCa also had LUTS. The fraction of the gland targeted for ablation ("ablation fraction) ranged from focal (12% ablation fraction) to whole-gland (98%) [Dora *et al*, 2022].

From Dora *et al*, the PSA improvement from baseline up to 5 years including focal to whole-gland ablation plans was 54%-97%. The rate of salvage treatment after one TULSA treatment for primary PCa was 7%-33% [Dora *et al*, 2022]. Urinary symptoms were stable in men with good voiding function at baseline, and 85% of men with concurrent PCa and lower urinary tract symptoms met criteria for improvement [Dora *et al*, 2022]. Symptom relief in a small cohort of men with LAPC was observed [Dora *et al*, 2022]. For the two largest studies from the literature search (Pavlovich 2023, Muschter 2023; combined n=295), Grade 3 adverse events were incurred by 11/295 men (4%), with no rectal injury/fistula or Grade IV events.

Internet searches were performed by Luke Chung on 26 July 2024 and are summarized in Table 3. From the FDA website, there was one record related to the TULSA-PRO system. This was an injury event on Apr 30, 2024 described as “prolonged increased pain post-TULSA”. Since the initial report, the patient has undergone placement of a suprapubic catheter and their pain was resolved. The suprapubic catheter, however, is intended as a temporary measure and pain specialists are currently consulting on the case to assess whether definitive pain relief can be achieved without the need for catheterization by use of nerve block therapies. Gastroenterology consultation was also requested. Intraprocedural imaging and contrast-enhanced MRI acquired immediately after the procedure revealed no evidence of overheating and confirmed a conservative ablation plan. There was no heating outside the prostate capsule. The post-treatment MRI also shows no evidence of bladder or rectal injury. There was no significant motion observed during the treatment. Investigation is ongoing.

Of the recall notices retrieved, one was a Class I recall related to another MRI-guided thermal therapy procedure (Monteris Neuroblate System) and two were Class II recalls related to EDAP Ablatherm and Sonalleve. While the indication and recalled heating device were very different from TULSA-PRO, these records related to MR-guided laser ablation were evaluated further in an attempt to identify any unforeseen risks that may also apply to the TULSA-PRO device.

There were no records of the TULSA-PRO system on the following international databases: German Federal Institute for Drugs and Medical Devices (2 records for Sonalleve MR-HIFU and 4 records for ProRhythm ablation catheter ProMap), United Kingdom Alerts, recalls and safety information: drugs and medical devices, and on the International Medical Devices Database (1 record for Ablatherm HIFU, and 10 record for Sonalleve MR-HIFU).

From the NIH clinical trials database <clinicaltrials.gov>, the search terms identified 10 clinical trials related to MR-guided transurethral ultrasound ablation of prostate tissue and are included for further evaluation (Table 4). These include four sponsored trials (the Phase I study, the TACT pivotal study, the CAPTAIN randomized controlled trial, and the CARE registry), and six investigator-initiated studies. The post-market surveillance data available from these studies are included in the evaluation.

Table 3. Results of internet searches.

Website	**Description**	**Search criteria**	Records	**Records on TULSA**
www.clinicaltrials.gov	NIH clinical trials database	Other terms: transurethral ultrasound prostate	49	10
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.cfm	FDA MAUDE database (Manufacturer and User Facility Device Experience)	Manufacturer: Profound Brand Name: TULSA, transurethral ultrasound, transurethral ablation, MR-guided, MRI-guided, HIFU	1	1

Website	Description	Search criteria	Records	Records on TULSA
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm	FDA Medical Device Recalls database	Product: TULSA, transurethral ultrasound, MRI-guided, MR-guided, HIFU, high-intensity ultrasound, ultrasound ablation Firm: Profound Reviewed all recalls for devices matching the keywords above.	0	0 TULSA 1 related to MR-guided laser ablation, 2 related to HIFU

Table 4. Clinical trials related to TULSA-PRO listed on NIH clinical trials database and sponsor database.

Study Title	Status	Conditions	Sponsor	Data Available
NCT02766543: Pivotal Study of MRI-guided Transurethral Ultrasound Ablation in Patients With Localized Prostate Cancer	Active, not recruiting	Prostate Cancer	Profound Medical Inc.	Post-market surveillance 12-month safety and performance data
NCT01686958: Safety Study of MRI-guided Transurethral Ultrasound Ablation of Prostate Tissue to Treat Localized Prostate Cancer	Completed, Has Results	Prostate Cancer	Profound Medical Inc.	12-month safety and performance data (Chin et al, Euro Urol 2016) 3-year post-market clinical follow-up (Nair et al, 2021) 5-year phase I study outcomes (Hatiboglu *et al* J Urol Open Plus 2023)
NCT03350529: MRI Guided Transurethral HIFU for Various Prostate Diseases	Active, not recruiting	Localised Prostate Cancer, Locally Advanced Prostate Cancer, Locally Recurrent Prostate Cancer, Benign Prostatic Hyperplasia	Turku University Hospital	Publications and conference abstracts as reported in systematic literature search
NCT03996005: MRI- Guided Transurethral Ultrasound Ablation of Localized Prostate Cancer	Recruiting	Localized Prostate Cancer	University Hospital, Strasbourg, France	Post-market surveillance
NCT03814252: Prospective Clinical Safety and Efficacy Study of Lesion-targeted MRI-TULSA for Localized Prostate Cancer	Active, not recruiting	Localized Prostate Cancer	Turku University Hospital	Post-market surveillance
NCT04808427: Pilot Study to Investigate Magnetic Resonance (MR) Image Guided Focal Therapy in Prostate Cancer	Not yet recruiting	Localized Prostate Cancer	National Cancer Institute	Post-market surveillance when data is available

NCT05438563 MRI-Guided Transurethral Urethral Ultrasound Ablation for the Treatment of Intermediate Grade Prostate Cancer	Recruiting	Localized Prostate Cancer	Mayo Clinic in Rochester	Post-market surveillance
NCT 05001477 Customized TULSA-PRO Ablation Registry	Recruiting	Localized Prostate Cancer	Profound Medical Inc.	Post-market surveillance
NCT05027477 A Comparison of TULSA Procedure vs. Radical Prostatectomy in Participants with Localized Prostate Cancer (CAPTAIN)	Recruiting	Localized Prostate Cancer	Profound Medical Inc.	Post-market surveillance
NCT05917860 Neoadjuvant ADT With TULSA in the Treatment of Intermediate Risk Prostate Cancer (NeoADT-TULSA)	Recruiting		Turku University Hospital	N/A
NCT06270043 Focal Therapy for Localized Prostate Cancer	Recruiting	Localized Prostate Cancer	University of California, San Diego	N/A
NCT03668652 Focal Prostate Ablation Versus Radical Prostatectomy (FARP)	Unknown	Localized Prostate Cancer	Oslo University Hospital	As described in specialist literature
NCT06223295 Effectiveness of Focal Therapy in Men With Prostate Cancer (ENFORCE)	Recruiting	Localized Prostate Cancer	Radboud University Medical Center	N/A

For Europe, where the 12-month Phase I outcomes were used as the basis for CE Mark, post-market surveillance data [e.g. DOC-12146, DOC-12557, DOC-13317] relevant to TULSA-PRO safety is available from the TACT clinical study, long-term follow-up from the Phase I study, and commercial treatments performed in Europe. As described in the TULSA-PRO Clinical Evaluation Report (GCP-10102), investigators in the TACT pivotal study reported 10 serious attributable adverse events across 7/115 (6.1%) patients.

By five years in the pivotal study, there was no grade ≥ 4 adverse event, no intraoperative complications, no rectal injury, no rectal fistula. There were 12 Grade 3 (severe) events in 9 men (7.8%) with onset and resolution by 1 year and 2 Grade 3 events in 2 men (1.7%) with onset between 1-2 years. Grade 2 (moderate) events included Urinary tract infections (25%), urinary retention (9%), abdominal or rectal discomfort (3.5%), urethral stricture (2.6%) all resolved

by 1 year. The rate of moderate incontinence (G2, pads indicated) was 2.6% at 1 year, and ongoing in 2 (1.7%) men by 5 years. There was continued recovery of erection firmness sufficient for penetration (78% at 4 years, 77% at 5 years), and IPSS and EPIC bowel domain scores stable between baseline and five years. For TACT 2.0, there were 3 Grade 3 (severe) adverse events in 2 patients (5.2%) which included sepsis, deep vein thrombosis, and urinary incontinence. 1 attributable SAE was reported which involved sepsis secondary to UTI which resolved with medication, catheterization, and hospitalization.

Preliminary results (pending source data verification) of the CARE Registry showed Grade III (Clavien-Dindo) complications in 5 men (2.6%) which included urethral stenosis resolved by cystoscopy, erectile dysfunction resolved by penile implant, bladder neck contracture and urinary retention resolved by cystoscopy, calculus in bladder resolved by transurethral resection of the prostate (TURP), and ongoing urethral stenosis and urinary incontinence managed by cystoscopy and insertion of artificial urinary sphincter respectively. No grade ≥ IV complications. SAEs related to TULSA occurred in 2 men which involved hypothermia managed by overnight hospitalization for observation and stenosis managed by incision with laser vaporization of prostate to prevent life-threatening impairment.

Preliminary results (pending source data verification) of the CAPTAIN study showed 3 SAEs in 2 patients related to device/procedure which involved worsening urethral stricture, rigid urinary sphincter, and prolonged increased pain. There was 1 SAE related to catheter which involved urinary tract infection managed by hospitalization and medication.

From the investigator-initiated studies (NCT03350529; NCT03814252), there were no ≥Grade 4 adverse events in primary PCa, salvage, and Benign Prostatic Obstruction (BPO) (n=60, n=41, and n=30) [Yli-Pietilä *et al* 2024, Anttinen *et al* 2024B, Anttinen *et al* 2024C]. For the study of focal TULSA (NCT03814252), there were 33 grade 2, 3 grade 3, and no grade 4 or above adverse events reported [Yli-Pietilä *et al* 2024]. For the study of TULSA for various diseases, BPO arm (NCT03350529**)**, there were 8 Grade 2 and 1 Grade 3 (including UTIs, retention, and epididymitis) which all resolved within 3 months of treatment [Anttinen *et al* 2024B]. For the radiorecurrent PCa arm of this study, there were 17 Grade 2 (related to urinary retention and UTI resolved by antibiotics and catheterization) and 2 Grade 3 (related to urinary retention treated with SPC and stents) [Anttinen *et al* 2024A]. From the European clinical service reports, Engelage et al reported Grade 3 adverse events in 7 patients, resolving within 3 months with no grade 4 or above complications.

In complaints data reported to the manufacturer from commercial treatments 1 serious and 5 non-serious incidents were reported at the last Post-Market Surveillance meeting in October 2024. The six non-serious incidents include: urethral stricture, urinary incontinence associated with pre-existing condition, bladder wall inflammation resolved by foley catheter, urinary tract infection resolved by antibiotics and transurethral resection to clear out necrotic tissue, and burning of prostatic urethra related to treatment interruption with no device fault The one serious incident involved prolonged increased pain post-TULSA. Patient was suffering with severe bladder neck spasms (UNK-Apr-2023) and rectal spasms (20-Jun-2023) since shortly after catheter removal (15-Mar-2023) post TULSA procedure (01-Mar-2023). This SAE was reported to OCREB on 02-May-2024. Patient has since received multiple catheterizations, is on medications such as ketorolac and botox injections for his spasms and undergone cystoscopies and bladder neck resection on 11-Apr-2024, with no improvement. Investigation is currently in progress. Preliminary results do not provide evidence of device malfunction. No new risks were identified, which did not change the overall risk/benefit assessment of TULSA-PRO treatment.

The internet search described in this section identified no safety-related events directly associated with TULSA-PRO. An FDA Class I recall related to MR-guided laser ablation of brain tissue was identified in the internet search and is investigated further here. The FDA recall (#Z-0194-2018), and two letters to health care providers (dated 22 March and 24 April 2018), raised concerns that 1) inaccuracy of MR thermometry may have resulted in underestimated

thermal damage, and 2) that MRI-induced heating of a thermocouple in an interstitial laser probe may have resulted in damage to the probe while in the patient. Both issues may have been linked to various neurological adverse events, and possibly patient death. In the first letter, FDA identified that MR thermometry uncertainty as high as 32°C was associated with the confluence of low temperature mapping spatial resolution, slow update rate, fast laser-induced heating rate, and lack of MR thermometry monitoring of post-ablation tissue cooling. These technical concerns are avoided in TULSA-PRO treatment due to a faster update rate (6 vs. 8 seconds), slower heating rate (approximately 2°C per second vs. 4°C per second), and continued MR thermometry to measure thermal dose accumulated during tissue cooling. The second concern raised by FDA is also not applicable to the TULSA-PRO system, as the TULSA-PRO applicator does not incorporate a metallic thermocouple that could heat surrounding tissue or the applicator itself upon interaction with the MRI. The clinical risks related to both concerns are also much lower for the indication of prostate ablation vs. brain. Unintended ablation of prostate tissue within the region of peak heating rates does not pose any serious risks to the patient, as opposed to unintended heating in the complex vasculature and eloquent parenchyma of the brain. For these reasons, the concerns raised by the FDA in the recall of the Monteris MR-guided laser interstitial thermal therapy device do not represent unforeseen risks associated with the TULSA-PRO.

5.4. An overall summary of clinical performance and safety

The TULSA-PRO® product literature and instructions for use are consistent with the clinical data in this report covering all the hazards and other clinically relevant information that may impact the use of the device. Any specific labeling required to mitigate hazardous situations has been included in the User Manual. Training of the end-user is required to ensure the safety characteristics and intended purpose of the TULSA-PRO® device. Prostate cancer is prevalent condition affecting men. The TULSA-PRO® device offers a minimally invasive, incision-free, image-guided method to safely ablate prescribed prostate tissue with an accuracy and precision of 1 mm. The accurate and precise cell kill of benign and malignant prostate tissue has been validated, demonstrating complete cell kill including tumor. Prospective clinical datasets further confirmed the TULSA-PRO® device performance, demonstrating fast conformal thermal ablation of prescribed prostate volumes with an accuracy and precision of 1 mm, as well as a favorable side-effect profile with minor impact on urinary, erectile and bowel function, specifically, near important structures such as the external urinary sphincter, neurovascular bundles and rectum. The TULSA-PRO® provides effective prostate ablation with local control of clinically significant disease, significant volume reduction, significant PSA reduction and low rates of residual cancer. The clinical evidence demonstrates the safe and effective performance of the device conforming to relevant Essential Requirements, the intended use and documented claims. The risks associated with the use of TULSA-PRO® are acceptable when weighed against the benefit. All risks identified in the risk management documentation have been addressed by the clinical data. Any specific labeling requirements to mitigate hazardous situations have been included in the User Manual. In summary, the TULSA-PRO® device is safe and effective to ablate prescribed prostate tissue in adult men. All identified risks associated with the device and ablation procedure were mitigated.

5.4.1. Safety requirements

5.4.1.1. Safety population in clinical studies

A total of 696 men have been treated with the TULSA-PRO or its equivalent prototype system across 26 completed clinical studies in men with localized prostate cancer (primary or recurrent), benign prostatic hyperplasia, or locally advanced prostate cancer. An additional 38 men have been treated with TULSA-PRO in the TACT 2.0 study and for whom manufacturer-held, unpublished adverse event data is available. Overall, 722 men are included in the safety population from clinical studies.

The primary clinical data used to evaluate the safety of the TULSA-PRO system is the TACT pivotal clinical study, which evaluated safety and ablation efficacy in 115 patients with mostly intermediate-risk disease who were treated with the intent of whole gland ablation sparing the urethra and external sphincter.

Safety data from the TACT pivotal study are supported by clinical data from the Phase I study, which evaluated safety and device performance in 30 patients with mostly low-risk disease, using conservative treatment parameters that intentionally spared 10% of the viable prostate volume. Two earlier treat-and-resect studies, which treated 8 and 5 patients respectively, provide data on the immediate tissue ablation performance but do not provide meaningful safety data because the men underwent prostatectomy immediately after TULSA.

The safety data are grouped according to clinical study (TACT, Phase I, and investigator-initiated), with primary focus on the TACT pivotal study and integrate the post-market follow-up data from the respective study.

On the basis of the latest PMCF studies, there were no updates to the risk management file and the conclusions derived from the PMCF studies did not result in any need for corrective or preventive actions. The PMCF report concluded that the risks associated with the TULSA-PRO device continued to be acceptable when weighed against the benefits to the patient, were compatible with a high level of protection and safety, were accurately described in the TULSA-PRO literature, and compared favorably to devices with similar intended use.

The periodic safety update report reviewed data from the post-market surveillance meeting, the post-market clinical follow-up report, and risk management production and post market monitoring report, and also concluded that there was no change in the type, severity, or frequency of adverse events related to TULSA-PRO, no change to the overall risk profile or performance of the device, and no change to the benefit-risk assessment of TULSA-PRO.

5.4.2. Risk Benefit Profile

The information presented here supports conformity to MDD ER1 /MDR GSPR3 with traceability to the risk management documentation.

For men with localized prostate cancer undergoing ablative therapy, the most relevant clinical endpoints were identified to be PSA reduction and the presence of clinically significant disease on 12-month biopsy. As described, the PSA reduction and rate of clinically significant positive biopsy after TULSA-PRO ablation in men with localized prostate cancer were comparable to standard of care external beam radiation therapy and benchmark prostate ablative devices.

The TULSA-PRO device offers a novel, minimally-invasive, image-guided method to safely ablate target tissue within the prostate gland with an accuracy and precision of 1 mm. The accurate and precise cell kill of benign and malignant prostate tissue has been validated, demonstrating complete cell kill including malignancy (GCP-10102). Two comprehensive prospective clinical datasets have further confirmed the TULSA-PRO device performance, demonstrating fast conformal thermal ablation of target prostate volumes with an accuracy and precision of 1 mm, as well as a favorable side-effect profile with rates of adverse events affecting urinary, erectile and bowel function comparable to or better than the standard of care interventions.

5.4.2.1. **Benefit-Risk Analysis**

The current knowledge of the state of the art, the available clinical data and evidence, the documentation including the Instructions for Use, and the risk management documentation were found in alignment. A benefit-risk analysis was performed for all risks that remained in the "Unacceptable" or "Further Analysis Required" category Potential harms related to these residual risks are included in the comparison of the TULSA-PRO safety profile to the standard of care. This analysis indicated that TULSA-PRO has a favorable safety profile compared to SOC treatments for localized prostate cancer. This clinical data was supported by the post-market surveillance in concluding that the incidence of the remaining harms has been adequately minimized by the instructions, cautions, and warnings in the TULSA-PRO literature. From available scientific literature, clinical evidence, the feasibility study, Instructions for Use, risk management documentation, and the safety and efficacy assessment, the risks associated with the use of TULSA PRO are found to be acceptable relative to the probable benefit. The probable benefit outweighs the overall residual risk from TULSA therapy, taking into account the probable risks and benefits of state-of-the-art treatment.

This clinical evaluation demonstrates that the risks associated with the TULSA-PRO device, described in the risks management documentation are acceptable when weighed against the benefits to the patient, and are compatible with a high level of protection and safety. The intended use, residual risks, and information to reduce the risk of use error, are accurately described in the TULSA-PRO product literature and instructions for use [102301].

5.4.2.2. Benefit-Risk Conclusion

The risk profile presented in this report supports the assertion of safe and effective performance of the TULSA-PRO device conforming to relevant Essential Requirements (DOC-10547)/MDD ER1 (MDR GSPR3), and the intended use and claims as documented in this Clinical Evaluation Report (GCP-10102) based on comparison with state of the art, clinical data of the device and risk management file.

All risks identified have been addressed by the clinical data, and any specific labeling required to mitigate hazardous situations has been included in the Instructions for Use (102301). In summary, the TULSA-PRO device is safe and effective to ablate target prostate tissue in adult men and risks associated with the device and ablation procedure have been identified and reduced to acceptable levels or justified to be acceptable when weighed against the clinical benefit.

5.4.3. Performance

The information presented here supports conformity to MDD ER3 / MDR GSPR1. The available data allows evaluation of performance, and there is sufficient clinical evidence for every intended performance.

5.4.3.1. Device performance population

A total of 158 localized prostate cancer patients were treated with the TULSA-PRO or its equivalent prototype system across four completed clinical studies in which performance, measured by thermal cell kill, prostate volume reduction and treatment time could all be assessed: the TACT study [Klotz et al 2021], the Phase I study [Chin et al 2016] and two Phase 0 studies [Chopra *et al* 2012, Ramsay *et al* 2017]. Together these studies provide comprehensive clinical evidence of device performance (conformal thermal ablation) and specific claims of cell kill, ablation accuracy and precision, prostate volume reduction and treatment time. All patients who were treated with the TULSA-PRO or its equivalent prototype in these completed clinical investigations are included in the device performance analysis, though a primary dataset (Phase 0, Phase I or TACT) is identified for each performance claim. In addition to the

evidence provided here in claims of prostate tissue ablation, benign and malignant, are further supported by clinical data from the literature (Section 5.3.4)with PSA reduction.

5.4.3.2. Prostate volume reduction

Prostate volume reduction was measured in the TACT and Phase I studies demonstrating effective ablation of the prescribed volume, which included both benign and malignant tissue [Klotz et al 2021; Chin et al 2016]. The TACT study represents the primary dataset for evidence of ablation effectiveness by prostate volume reduction, since the planned ablation extended to the prostate capsule. Furthermore, as per protocol, the TACT study employed a central radiology core lab to measure prostate volume prior to and after treatment with TULSA-PRO, providing consistent methodology and reducing inter-observer variability. The Phase I study represents a supportive dataset since the planned ablation represented only 90% of the prescribed prostate tissue volume, and while a central radiologist assessed the volume changes this was not specified a prior in the study protocol. In both the TACT and Phase I studies, measures of prostate volume reduction were obtained by comparing the volume of perfused prostate glandular tiss e prior to treatment with the TULSA-PRO, to those obtained on MRI at 12-month follow-up.

In the TACT study, 106 of the 115 patients had MR image data prior to and after TULSA (at 12 months) that were available and readable by the central radiology core lab. Based on the per-protocol assessment from a central radiology core lab, the median (IQR) perfused prostate volume of patients in TACT decreased 91.4% from 37.3 (27.2 – 47.6) cc pre-treatment to 2.8 (1.7 – 4.7) cc at 12 months on MRI. Given the treatment intent of whole-gland ablation with sparing of the urethra and urinary sphincter, the prostate volume reduction measurements demonstrate effective prostate tissue ablation of the TULSA-PRO.

In the Phase I study, MRI and transrectal ultrasound-guided prostate biopsy at 12 months show diminutive prostate volumes, averaging 51% fibrosis (n=29). The median reduction in viable prostate volume was 88%, in excellent agreement with predictions based on MR thermometry (90%) and the planned prostate ablation volume (90%) [Bonekamp *et al* 2018].

5.4.3.3. Treatment time

TULSA-PRO treatment time is defined as the amount of time required to deliver the ultrasound energy to the prescribed prostate volume. The TACT study represents the primary dataset to evaluate treatment time, as the Phase I study used conservative treatment margins, and the Phase 0 studies targeted small sub-volumes of the prostate (average time 15 min [Chopra *et al* 2012]). In the TACT study, the median (IQR) ablation time was 51 (39-66) min for a median 40 (32–50) cc prostate volume (1.3 min / cc). Phase I TULSA-PRO average treatment time was 36 min for average 48 cc prostate volume, with large 90 cc prostates taking up to 60 min (Figure 24). These fast treatment times are in stark contrast to SOC treatments of localized prostate cancer as well as other ablative devices such as transrectal HIFU that take upwards of 2 to 3 hours to ablate small 25 cc prostate volumes [Blana *et al* 2004, Uchida *et al* 2006].

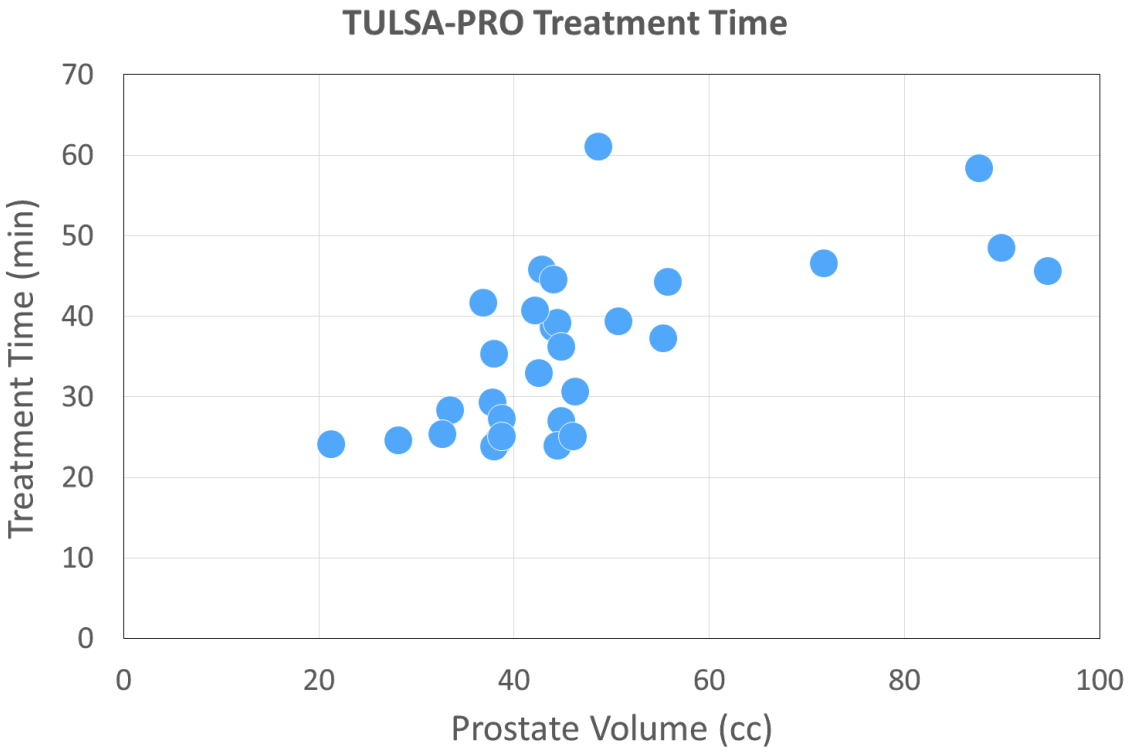


Figure 5. TULSA-PRO treatment time as a function of prostate volume, obtained from the Phase I study.

5.4.4. Clinical benefits

TULSA-PRO safety and device performance were assessed in Section 5.4.1 and 5.4.3. In addition, clinical benefits including PSA reduction, histological response on follow-up prostate biopsy, and alleviation of lower urinary tract symptoms were assessed either as specific primary and secondary endpoints or exploratory analysis of the TACT and Phase I studies. Alleviation of lower urinary tract symptoms, PSA reduction and the rate of salvage treatment were assessed in clinical data from the literature. These clinical benefits are summarized in Section 5.2.2, Section 5.2.3, and Section 5.3.

5.4.5. Acceptability of side-effects

Information presented in this section supports conformity to MDD ER6 / MDR GSPR8

The TULSA-PRO has a well-tolerated side-effect profile, as evidenced by the absence of CTCAE Grade ≥ 4 AE, the very low rates of attributable Grade 3 AE, the very low rates of SAE, and the nature of acute Grade 2 AE which mostly resolve by 12 months post-treatment.

The low morbidity of the TULSA-PRO is in contrast to Standard of Care (SOC) treatments for localized prostate cancer, such as Radical Prostatectomy (RP), External Beam Radiation Therapy (EBRT), Brachytherapy (BT) and High-Intensity Focused Ultrasound (HIFU). Table 35 compares the rates of salvage treatment, severe urinary incontinence, urinary strictures, GI toxicity and erectile dysfunction between SOC treatments and the TULSA-PRO. Due to the high variability

and non-standardized methods of data collection, naming conventions and follow-up reporting of SOC treatments for localized prostate cancer, a comprehensive analysis was performed generating a "primary value" and "range" for each treatment and associated complication. While this comparison does not use matched populations, the analysis is deemed appropriate as side-effects and treatment-related morbidity are independent of patient baseline prostate cancer characteristics for organ-confined localized disease. In fact, the older population included in the TULSA-PRO TACT and Phase I studies is likely to have higher, if not similar, rates of baseline co-morbidities and reduced ability to recover post-treatment.

Complication	Treatment	Primary Value	Range	Notes: Reference numbers are in square brackets and are listed below the table. • [1] Complication range values obtained from assessment of Figures 3 to 5 in the reference
Severe Urinary Incontinence	RP	15.3% [2]	0% to 50% [1]	• [2] Table 1: Adjusted values for "No control or frequent leaks".
	EBRT	4.1% [2]	2% to 15% [1]	
	BT	6% [5]	0% to 15% [1] 0% to 18% [4] 6% to 13% [5]	• [4] Refers to two studies reporting negligible (0%) to 18% (Kollmeier *et al* 2005). • [5] Leak at least daily: 11% overall, 6% (recent implants), and 13% (older implants).
	HIFU	11% [6]	5% [7] to 22% [8]	• [6 summary] 16 patients (pts) (moderate) + 3 pts (severe) / 135 total pts = 14% urinary incontinence, with 11% ongoing at 24 months. • [6 slides] 10% moderate to severe urinary incontinence. • [7] 5% Stress 2/3 urinary incontinence, and 19% Stress 1. • [8] 44 pts (total pts with incontinence) – 22 pts (mild incontinence) / 100 total pts = 22% urinary incontinence. Note that these are salvage radiotherapy failure patients.
	TULSA-PRO	3%		• No reports of severe urinary incontinence. • Grade 2 urinary/urge incontinence: 7 patients (6%). • Grade 1 urinary or urge incontinence: 21 patients (16.5%). • Ongoing at 12-month follow-up visit: 9 patients with Grade 1 incontinence (7.8%), 3 with Grade 2 (2.6%). • The proportion of patients preserving social continence (EPIC Q5≤1 pad/day) was 97% at five years.
Urinary Stricture (requiring treatment or moderate to severe)	RP	9% [3]	0% to 9% [1] 3% to 26% [3]	• [3] Table 3: Selected 1-year data to be consistent with TULSA-PRO data, though incidence of stricture increases over time. • [3] References reported stricture rates of 3%-26% after RP, 9%-12% after BT, 2% after EBRT.
	EBRT	2% [3]	0.8% to 9% [1]	
	BT	6% [3]	1% to 25% [1] 9% to 12% [3]	
	HIFU	27% [6]	9% [7] to 35% [6]	• [6 slides] 27% moderate to severe stricture, 35% total strictures (various urinary locations). • [6 summary] Describes 26 pts /135 pts = 19% pts with urinary stricture: 5 mild, 19 moderate, 7 sever. Lower bound for moderate to severe stricture: 26 pts – 5 pts (mild) / 135 pts = 15.6%. • [7] 9% late stenosis.
	TULSA-PRO	2.6%		• Two reports of Grade 3 urethral stricture (1.7%), resolved with TURP. • One report of a Grade 2 urethral stricture (0.9%), resolved with TURP.
GI Toxicity (diarrhea, bowel urgency, painful hemorrhoids)	RP	15% [2]	0% to 15% [1] 10% to 24% [2]	• [2] Table 1: Approximate average for "diarrhea", "bowel urgency" and "painful hemorrhoids". • [4] Supports this value. For example, Kuban *et al* (2008) reported GI RTOG ≥ 2 events were 28%, for 3D conformal RT with 78 Gy.
	EBRT	25% [2, 4]	0% to 40% [1] 20% to 27% [2]	
	BT	9% [4]	0% to 25% [1]	• [4] Describes study by Zelefsky *et al* (2000) with late Grade 2 rectal bleeding of 9%.
	HIFU	7% [6]	1% to 21% [6]	• [6 slides] 7% moderate or severe GI dysfunctions related to device or procedure; 21% all bowel dysfunction AE; 4% non-serious bowel injury. While no fistulas observed in IDE population, 1+% reported in supporting patient data sources. • [7] 0.7% rectal fistula rate for modern HIFU treatments (2005 – 2009). • [8] Moderate and severe GI events total 33%, excluding oral-related events (chipped tooth, dental caries, oral pain) and constipation. Serious GI events include rectal fistula (5% patients) and small intestine obstruction (1%). Note these are salvage radiotherapy failure patients.
	TULSA-PRO	0%		• No reports of attributable Grade > 2 GI AE. • Very few Grade 2 GI attributable AE, which may not be directly related to TULSA-PRO, but incidental to the bowel preparation, anesthesia, and GI anti-spasmodic drug used during treatment: Four patients with Grade 2 pain/discomfort (3.5%), two patients with Grade 2 nausea (1.7%), and one with Grade 2 constipation (0.9%), all resolved within 6 weeks.

Erectile Dysfunction (erections insufficient for penetration or intercourse)	**RP**	79.3% [2]	25% to 100%[1]	• [2] Table 1: Adjusted values for "erections insufficient for intercourse".
	EBRT	63.5% [2]	7% to 85% [1]	
	BT	58% [4]	13% to 60% [1]	• [4] Refers to Bottomley *et al* (2007), where from fully potent patients at baseline, 42% patients were able to achieve erections sufficient for intercourse post-treatment.
	HIFU	58% [7]	44% to 67% [6]	• [7] Median IIEF-5 score decreased from 17 to 5 ($p < 0.001$). Potency (IIEF ≥ 17, mild or no ED) was preserved in 42.3% of patients with a baseline IIEF score ≥ 17 (58% ED). • [6 summary] 67% ED (any occurrence) and 44% (ongoing at 24 months). Minimum bound on moderate to severe ED: 91 pts (total with ED) – 21 pts (mild ED) / 135 total pts = 52% ED. • [7 slides] 52% moderate to severe ED.
	TULSA-PRO	13%		• Proportion of patients with erections sufficient for penetration decreased 25% from 92/111 (83%) at baseline to 70/111 (63%) at 12 months. 40/52 subjects (77%) with erections sufficient for penetration at baseline also maintained erection firmness by 5 years.
Rate of Salvage Treatment	**RP**	18% [10]	16% to 27% [10]	• [10] 39/246 (15.9%) of RP patients underwent salvage radiotherapy. Failure-free survival was 82% (77-88%) at 5 years based on their definition 1, 73% (67-79%) at 5 years based on their definition 2, and 73% (68-80%) at 7 years based on any post-operative radiotherapy after RP.
	EBRT	13% [11]	7% to 13% [11]	• [11] After 6 years, the estimated FFS was 87.4% (95% CI 79.9-93.9). Treatment failure (salvage treatment, metastases, systemic treatment, or watchful waiting) was reported in 7% of patients.
	HIFU	37% [8]	19% to 53% [8]	• [8] Median follow-up of 6.4 yr with a median dose of 72 Gy (range: 65-78). The 5-year additional treatment-free survival rates for low-, intermediate, and high-risk patients were 81%, 66%, and 47%, respectively.
	TULSA-PRO	22% [12]		• [12] By 5 years, 25 men (21.7%) underwent post-TULSA salvage (10 RP, 10 RT, 3 RT+ADT, 1 RP+RT). Repeat TULSA not permitted.

Table 35 References:

[1] Thompson (Chair) *et al* AUA prostate cancer clinical guideline update panel, "Guideline for the management of clinically localized prostate cancer: 2007 update," The Journal of Urology, 177: 2106-2331 (2007)

- Cite 357 times by other publications
- Represents the latest AUA guidelines
- Comprehensive literature review of 436 clinical reports
- The wide ranges are testament to the non-standardized methods used in the field: non-standardized data collection, naming conventions (definition variability) and follow-up reporting
- To our knowledge, this publication constitutes the best review of prostate cancer treatment outcome data
- Complication range values obtained from assessment of Figures 3 to 5 in the reference

[2] Potosky *et al,* "Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the Prostate Cancer Outcomes Study (PCOS)," Journal of the National Cancer Institute, 96(18): 1358-1367 (2004)

- Cited 293 times by other publications
- Major prostate cancer study (PCOS: Prostate Cancer Outcomes Study)
- PCOS designed to prospectively assess the longterm health-related quality-of-life outcomes
- Outcomes worsen over time as evidenced in: Resnick *et al* "Long-term function outcomes after treatment for localized prostate cancer," The New England Journal of Medicine, 368: 436-445 (2013)

[3] Elliott, Carroll *et al* and the CaPSURE Investigators, "Incidence of urethral stricture after primary treatment for prostate cancer: data from CaPSURE," The Journal of Urology, 178: 529-534 (2007)

- Cited 74 times
- Major patient database (CaPSURE: 6,597 men)
- Incidence of treatment for urethral stricture, including bladder neck contracture, after primary treatment for clinically localized prostate cancer.

[4] Budaus *et al*, "Functional outcomes and complications following radiation therapy for Prostate Cancer: a critical analysis of the literature," European Urology 61: 112-127 (2012)

- Cited 43 times
- Major review of 132 articles

[5] Talcott *et al* "Long-term treatment related complications of brachytherapy for early prostate cancer: a survey of patients previously treated" The Journal of Urology 166(2): 494-499 (2001)

[6] EDAP Technomed Inc., "EDAP Ablatherm® integrated imaging high intensity focused ultrasound (HIFU) indicated for the treatment of low risk, localized prostate cancer," Sponsor Executive Summary (June 23) and Presentation Slides (July 30) from the Premarket Approval Application P130003 (2014).

- Unless otherwise specified, data obtained from the IDE G050103 population (n = 135 patients)

[8] Crouzet *et al* "Whole-gland ablation of localized prostate cancer with HIFU: oncologic outcomes and morbidity in 1002 patients," European Urology 65(5): 907-914 (2014).
- Longest follow-up and largest cohort of HIFU treated patients
- Uses the EDAP Ablatherm device

[9] Sonacare Medical, "Sonacare Medical Sonablate 450 for the treatment of locally recurrent prostate cancer," Sponsor Executive Summary (Oct 1) from the Premarket Approval Application P130002 (2014).
- Data obtained from the IDE G080057 population (interim analysis of n = 100 patients)

[10] Shah *et al*, "Focal therapy compared to radical prostatectomy for non-metastatic prostate cancer: a propensity score-matched study," Prostate Cancer Prostatic Dis 24(2):567-574 (2021)

[11] van Son *et al*, "Conventional radical versus focal treatment for localised prostate cancer: a propensity score weighted comparison of 6-year tumour control," Prostate Cancer Prostatic Dis 24(4):1120-1128. (2021)

[12] Eggener et al, "Pivotal Study Of MRI-Guided Transurethral Ultrasound Ablation (TULSA) Of Localized Prostate Cancer: 5-Year Follow Up," Urol Oncol: Semin Orig Investig. Conference: SUO 24th Annual Meeting. San Antonio United States. 42(Supplement) (pp S83) (2024)

Table 5. Comparing the safety profile of SOC treatments for localized prostate cancer to the TULSA-PRO.

5.5. Ongoing or planned post-market clinical follow-up (PMCF)

PMCF plan describes the studies which will be conducted by Profound Medical to review TULSA-PRO® 's performance and safety, including long-term occurrence of clinical events in a more representative population of patients. The data and conclusions derived from the PMCF studies are assessed to find any undesirable side effects under normal conditions of use, and whether they constitute the risks when weighed against the intended performance of the device and compared to equivalent or similar devices: on risk management file and Clinical evaluation report. Addition Post market surveillance processes such as complaint handling, medical device reports, notices, recalls, corrective and preventive actions, and documentation, are described in the Post Market Surveillance Procedure. This PMCF will be reviewed annually during the Post Market Surveillance annual meeting and updated, if necessary. A report on PMCF outcomes including assessment of new product features is updated periodically.

Post-market clinical data are collected according to Post-market Surveillance Procedure [QMS-00653] and are summarized annually in the TULSA-PRO Post Market Surveillance Meeting Record [DOC-12557; DOC-13317; DOC-13769]. The summary includes updates from the Post-Market Clinical Follow-up Report (GCP-10274) and the Periodic Safety Update Report [DOC-12558, DOC-13315, DOC-13800]. The findings of the Post Market Surveillance Meeting are also summarized in the Risk Management Production and Post-Market Monitoring Report [DOC-12556, DOC-13316, DOC-13768]. These reports include trends related to any applicable incident reports, field safety corrective actions, and complaints, along with usage information and benefit-risk assessment. Results of this analysis are summarized in Section 4.2.6.

6. Possible diagnostic or therapeutic alternatives

The TULSA-PRO® system combines high intensity directional (but unfocused) ultrasound for tissue ablation, delivered through a transurethral applicator, and monitored in real-time using magnetic resonance imaging. The other marketed devices for prostate ablation do not incorporate these features. The same type of ablation and high intensity ultrasound is used by HIFU devices; however, these products use focused ultrasound and deliver energy to the prostate through the rectum. The same delivery approach (transurethral) is used by other devices but with different energy sources such as laser, RF or microwave.

Other devices in the market offer imaging feedback during ablation procedures, but none offer real-time imaging simultaneously during the ablation procedure with the same high resolution as is offered by TULSA-PRO® System through MR imaging.

The combination of these features differentiates the TULSA-PRO® System from other prostate ablation devices currently on the market.

7. Suggested profile and training for users

Profound Medical Inc. has developed a training program for professionals who will use the device. Training of the end-user is required to ensure the safety characteristics and intended purpose of the TULSA-PRO® device is achieved. The Organization has developed the following programs to achieve its objectives:

Learning objectives for Physician:

- TULSA-PRO Online Physician Training Webinars
- Physician Software Hands-on Training Session
- MRI Treatment Walkthrough or Case Observation

b. Learning Objectives for Technologist and support Staff

- TULSA-PRO Online Technologist Training Webinars
- MRI Equipment Setup Practice Session
- MRI Treatment Walkthrough or Case Observation

8. Reference to any harmonised standards and CS applied

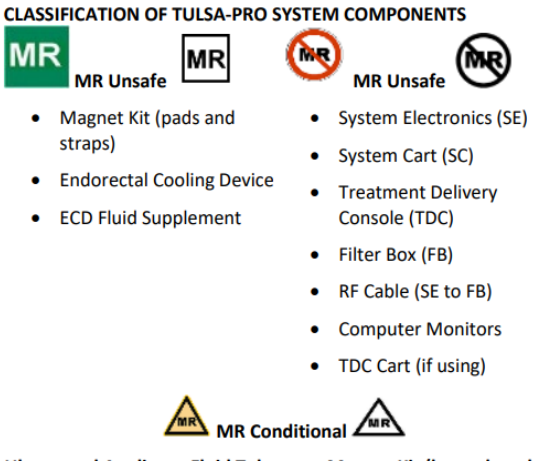
See Appendix B

9. Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
Rev: 01	March 10, 2025	Initial release of SSCP for TULSA-PRO®	☒ Yes Validation language: English ☐ No (only applicable for class IIa or some IIb implantable devices (MDR, Article 52 (4) 2nd paragraph) for which the SSCP is not yet validated by the NB

Appendix A. Warning and Precaution

Warning Label	Description
Patient Safety	MR-guided transurethral ultrasound therapy using the TULSA-PRO® System has inherent risks of complications. The TULSA-PRO® System and components should only be used in accordance with the intended use, indications for use, and instructions for use. Failure to do so could affect patient safety, cause insufficient therapy, or both.
Patient Motion	Successful targeting and treatment of the prostate gland, and avoidance of thermal damage to surrounding anatomy, depends on accurate Magnetic Resonance (MR) images of the patient. Once treatment planning has begun, patient motion (voluntary or involuntary) is not tolerated by the treatment planning or delivery software. You must be vigilant to watch for patient motion and must stop treatment if you see any patient movement
Damage to the External Sphincter	If the TULSA-PRO® Ultrasound Applicator (UA) is incorrectly placed or moves during treatment, the patient's external sphincter can overheat, causing temporary or chronic incontinence. Use MR images to check that the UA is correctly positioned and check MR images regularly during treatment delivery to ensure the UA has not moved. It is recommended that Operators read the TULSA-PRO® Operator's Manual to avoid external sphincter damage.
Damage to the Rectum	The Endo-rectal Cooling Device (ECD) must be correctly positioned in the patient's rectum (depth and orientation) to provide cooling to the rectal wall during treatment. Always use lubricant on the device and insert the ECD into the rectum only until resistance is felt. Rectal perforation requiring surgical intervention can occur if the ECD is inserted with too much force. The ECD must be completely free of air bubbles to avoid absorbing ultrasound energy. Use MR images to check that the ECD is correctly positioned and check MR images regularly during treatment delivery to ensure the ECD has not moved.
Strong Magnetic Fields	The TULSA-PRO® System is designed to operate together with a Magnetic Resonance scanner. The patient, system Operators, and health care personnel must be screened before entering the MR environment. All equipment entering the MR environment will be subject to strong magnetic fields and must be approved by Profound Medical before use. All TULSA-PRO® System equipment is specifically identified as MR Safe, MR Conditional, or MR Unsafe for use in the MR environment. To learn a device or component's MR safety rating, check the labels on the component and its package (see List of Symbols). All health care personnel and system Operators must be vigilant to ensure that only approved tools, medical supplies, and equipment are brought into the MR environment. Personal injury or equipment damage can occur if care is not taken



Ultrasound Applicator, Fluid Tube-sets, Magnet Kit (base plate, leg supports), Positioning System (PS), Positioning System Interface Box (PSIB)

These components have been tested in 1.5T and 3T MRI systems. Follow the TULSA-PRO Operator's Manual for equipment setup and usage instructions. UA Cable, PS Cable Use only the cables that ship with your TULSA-PRO system. These cables have been tested and are compatible with your MRI system. Do not transfer these cables to a different MRI system, or unexpected surface heating could result. Follow the TULSA-PRO Operator's Manual for equipment setup and usage instructions. RF Cable (FB to PSIB) • Cable must be installed according to the Equipment Setup section in the Operator's Manual • Cable must be attached and secured at both ends and must not be routed through the MRI bore. If the cable is not attached at both ends, the connector could be pulled into the magnet and cause damage to the MRI. If the cable is routed through the MRI bore, unexpected heating and patient injury could occur. The following conditions for safe use apply to the TULSA-PRO MR conditional components listed above:

• Static Magnetic Field Strength (B0): 1.5T and 3T (Refer to cable specific labeling for cable field strength)
• Type of Nuclei: 1H
• MR Scanner Type: Cylindrical Bore • B0 Field Orientation: Horizonal • Maximum Spatial Field Gradient: 4 T/m
• Max Gradient Slew Rate: 200 T/m/s
• RF Excitation: Circularly Polarized
• RF Transmit Coil Type: Integrated Body Transmit Coil
• RF Receive Coil Type: array coils placed anterior and posterior to the patient's lower abdomen • Maximum Whole-Body SAR: 2 W/kg • Patient Position: Patient supine, positioned as described in Operator's Manual • Image Artifacts: Device may produce image artifact

b. Cautions Cautions are potentially hazardous situations, which, if not avoided, could cause minor or moderate injury. They are also used to alert against unsafe practices. The following is a list of precautions for safe and effective operation of the TULSA-PRO® System.	
b.i Equipment Set Up	
Caution	Description
Installation and Testing	The TULSA-PRO® System must be installed and tested before use by a representative of Profound Medical
Equipment Storage Conditions	Refer to Operating and Storage Conditions for acceptable temperature and humidity storage conditions for the TULSA-PRO equipment. **Capital Equipment** - You must report exclusions from these conditions to an authorized Profound Medical service representative. Equipment requires testing to confirm functionality. **Disposable Devices** - Devices exposed to extreme temperature excursions must not be used, due to unknown effect on device performance. Contact your local sales or clinical representative to replace these devices.
Equipment Storage	The TULSA-PRO® System must be stored in a location with restricted access to avoid unauthorized modification of the system components or tampering with software
IT Networks	The TULSA-PRO® System is installed and validated on the IT network in the hospital or clinic organization. Personal health information is transferred through this network. Connection to a different IT network or changes to the IT network could cause previously unidentified risks to patients, Operators, or third parties, including exposing personal health information to unauthorized users. Changes to the IT network include: • changes in network configuration • connection of additional items • disconnection of items • update of equipment • upgrade of equipment. The hospital or clinic organization is responsible for identifying, analyzing, evaluating, and controlling these risks
External Removable Devices	USB ports found on the TDC computer are a source of potential cybersecurity threats. If tampering is evident or suspected, contact Profound Medical for technical support immediately. When connecting external storage media to the TDC computer, ensure that it does not contain viruses or malware, which could infect the TDC computer and/or networks it is connected to. USB storage devices

	must be formatted to FAT, FAT32 or NTFS. BitLocker-enabled devices are supported and recommended for transferring files that may contain patient-health information (treatment reports and treatment videos)
Incompatible Equipment and Software Programs	The TULSA-PRO® System can malfunction if transmitting devices, such as mobile telephones or two-way radios including antennas, are used near the equipment. Devices must be no closer than 30 cm from any part of the system, including cables. Do not install any other software on the TDC computer; this can cause the TULSA-PRO® System to malfunction or be exposed to malware. You must quit all other applications and programs before starting the TULSA-PRO® software. Do not attempt to run other applications simultaneously or system function may be compromised. Do not adjust or replace the operating system of the TDC computer or install any software updates. This could cause the TDC software to malfunction. Only service personnel authorized by Profound Medical should set up and configure the TULSA-PRO® software. Do not run anti-virus scans on the TDC computer while running the TDC software because it can decrease performance. The TULSA-PRO® TDC computer does not support joining an Active Directory. Group policy changes may result in unexpected system behavior
Loss of Data	If the TULSA-PRO® System is switched off while the program is accessing the hard drive, data can be lost or corrupted. To prevent data loss or corruption, always exit the program before turning off the unit. IT professionals should back up data regularly and delete old data from the TDC computer
External Electronic Interfaces	Do not plug in USB devices to the TDC computer that are not external storage devices. Do not disconnect network cables during the operation of the TULSA-PRO® system, as it will likely result in a software alarm and unnecessary treatment delays.
Power Requirements, Voltage and Cabling	Use only the electrical power cables supplied with the TULSA-PRO® System. These cables are fitted with a hospital-approved, three pole plug with a protective ground conductor. Never use an extension cable with the main electrical power cable. The length of the extended cable increases the resistance of the protective ground conductor beyond an acceptable level. Never use the System Electronics on the same outlet as another high-current drawing device (such as an air compressor); this can cause over-loading of the circuit. Always keep power cables, sockets, and plugs clean and dry.
Grounding System	Only connect the equipment to an AC power supply that has a protective ground conductor in accordance with IEC requirements or applicable local regulations. The grounding system in the treatment area should be checked regularly by a qualified engineer or hospital safety personnel. Never interrupt the protective ground conductor inside or outside the equipment, or disconnect the protective ground

	terminal, or you are likely to make the apparatus dangerous to operate. The ground conductor must be checked regularly.
Do Not Stack Equipment	TULSA-PRO® system components should not be used adjacent to or stacked with other equipment and if adjacent or stacked use is necessary, the system should be observed to verify normal operation in that configuration in which it will be used.
Electromagnetic Compatibility (EMC	The TULSA-PRO® System needs special precautions regarding EMC and must be installed and put into service according to the EMC information described in Service and Maintenance. Only use the TULSA-PRO® System within a commercial or hospital MRI environment. The MRI environment should provide RF shielding effectiveness of minimum 80dB isolation from 2MHz to 128MHz. Portable and mobile RF communications equipment can affect the TULSA-PRO® System. The emissions characteristics of this equipment make it suitable for use in industrial areas and hospitals (CISPR 11 class A). If it is used in a residential environment (for which CISPR 11 class B is normally required) this equipment might not offer adequate protection to radio-frequency communication services. The user might need to take mitigation measures, such as relocating or re-orienting the equipment. Certain common low frequency, RF emitters, such as RFID systems operate at 134.2kHz and 13.56 MHz that are commonly used in professional healthcare facilities for inventory control and other device recognition purposes. This is a potential source of EMI (electromagnetic interference). DO NOT USE such RFID equipment in the vicinity of the TULSA-PRO during clinical operation
Lethal Voltages	The TULSA-PRO® equipment carries lethal voltages when connected to the electrical supply. Do not attempt to remove enclosure covers or attempt any repair or service activity, at risk of death or personal injury. Always contact Profound Medical for authorized maintenance or repair.
Replacing Fuses	The System Electronics power entry module contains two fuses that can be replaced by an Operator. Use the correct model number of replacement fuse depending on the jurisdiction of use: • North America: Two (2) 10A Fuses, 250VAC 5x20mm, Manufacturer Littelfuse, Part No. 0218010.HXP • European Union – Two (2) 5A Fuses, 250VAC 5x20mm, Manufacturer Littelfuse, Part No. 0218005.HXP Failure to use the correct fuse could cause an equipment fire or burn the Operator. ⚠ Never replace fuses while using the equipment with a patient
Potentially Explosive Environments	The TULSA-PRO® System is not designed for use in potentially explosive environments. Never operate it in the presence of flammable liquids or gases

Emission Levels and Degree of Immunity	The use of accessories and cables, other than those stated in the instructions given in this manual and provided by Profound Medical, can cause increased emissions or decreased immunity of the TULSA-PRO® System
Inspect Equipment Before Each Use	All components, cables, and accessories should be inspected for damage before each use. Contact a Profound Medical authorized service representative if you see damaged equipment.
Accessories, Transducers and Cables	Using accessories, transducers, and cables other than those specified, with the exception of transducers and cables sold by the manufacturer of the TULSA-PRO® System as replacement parts for internal components, can cause increased emissions and decreased immunity of the TULSA-PRO® System.
Coiling Electrical Cables	Do not coil electrical cables that are in the MR scanner room. RF heating of the cables can occur during MR imaging, resulting in a patient burn. Properly drape and pad the patient to ensure there is no direct patient contact with external equipment or cables
Electrical Connections to MRI Suite	Use only the grounded Filter Box provided to route electrical cables into the MRI suite. Failure to use the TULSA-PRO® penetration panel filter box can interfere with normal operation of the MRI system, which could cause corrupt MR images and inaccurate temperature measurements
Keep Fans Clear	The System Electronics enclosure has openings on the front and rear sides for air intake and air exhaust. Do not block these openings or the electronics could receive insufficient air flow for cooling, which can cause components to overheat and fail
Acceptable Ambient Temperature	The fluid flowing through the UA keeps the urethra cool, which helps protect urethral tissue. The ECD cools the rectal wall, which protects the rectum from heat damage. The UA and ECD fluids flow from IV bags that hang on the System Cart. Check the 'Operating Environment' in the Service and Maintenance to learn the acceptable ambient temperatures that will reduce the risk of tissue damage. If fluid temperatures are higher or lower than the specified range, you will see an Information message on the TDC Console.
Use Only Sterile Devices	The UA and UA Fluid Circuit tubing are sterile and intended for single use only. Never use devices that do not come from a sterile package. Inspect all sterile packages before opening and discard any packages that appear damaged in any way that could affect product sterility.
UA is Fragile	The UA is fragile and should be handled with extreme care. If dropped or handled roughly, internal components could be damaged in ways that are not obvious to an Operator. Do not use a UA if you suspect any damage.
Use Only Sterile Cooling Fluid	Use only the specified sterile water IV bags to fill the UA and ECD fluid circuit. Do not use saline IV bags; saline will interfere with the MR images used for temperature monitoring during treatment.

ECD Fluid	Good fluid flow in the ECD provides effective cooling of the rectal wall. Without continuous fluid flow, there is risk of unintended heating and thermal damage to the rectal wall, which may lead to unwanted medical intervention. To ensure proper fluid flow to the ECD, inject the ECD Fluid Supplement solution into the ECD sterile-water IV bag before filling the circuit (see 'Treating, or doping, the ECD circuit' in the TULSAPRO® Operator's Manual). If you do not add the correct volume of solution, the MR signal from the ECD will cause imaging artifacts. Once MR imaging starts, check that the water in the ECD appears black on the MR image. Without the additive, the water appears very bright. There must be no air bubbles in the cooling device. Bubbles reduce the cooling capability, which might cause imaging artifacts and unintended heating where the ultrasound interacts with the air bubbles  **Never put UA fluid into the ECD Circuit. ECD fluid is sterile water with manganese chloride added to minimize flow artifacts on MR thermometry imaging (and surfactants added to minimize bubble formation). Since the UA fluid (sterile water with no additives) does not contain manganese chloride, its use in the ECD may alter the rectal imaging characteristics (producing artifacts), which could impact rectal safety.**
Do Not Drink Fluid	The ECD Fluid Supplement solution provided for the ECD fluid circuit is not safe for drinking. Gastro-intestinal irritation can result if this fluid is ingested
UA Fluid	It is important to maintain good fluid flow in the Ultrasound Applicator (UA) in order to: 1. Cool the surrounding tissue of the urethra, which reduces post-treatment genitourinary complications. 2. Cool the active ultrasound transducer elements within the applicator. Improper cooling can damage transducers, and they would stop sending out power 3. Ensure that there is an uninterrupted, air-free path for ultrasound to travel from the transducer into the prostate.  **Never put ECD fluid into the Ultrasound Applicator. See 'Fluid preparation' in the TULSA-PRO® Operator's Manual for more about the risk**
Fluid Tube Setup	It is important to correctly set up and connect all fluid tube sets to ensure there is good fluid flow through the UA and ECD during treatment. If fluid flow is restricted, there can be overheating of the UA or ECD, which can cause thermal damage to tissue and anatomical structures beyond the prostate boundary or to the rectal wall, respectively. The System Cart will monitor the fluid pressure and volume, and a high pressure or low volume alarm might indicate

	interrupted fluid flow in the UA or ECD. For instructions on proper fluid tube setup, see 'System cart' in the TULSA-PRO® Operator's Manual.
No bubbles in UA and ECD	Ensure that no bubbles are inside the Ultrasound Applicator (UA) and the Endo-rectal Cooling Device (ECD). Always check for bubbles after purging the devices. Bubbles in the ECD can prevent adequate cooling of the rectal tissue and affect the accuracy of the thermometry in the surrounding tissue. Bubbles in the UA can deflect the ultrasound to heat tissue outside of the intended treatment volume or prevent adequate heating of the intended treatment volume.
Air in Fluid Circuit Line	Take care not to introduce air bubbles in the fluid lines after they are purged during system setup. Any air bubbles that remain in the lines could interfere with ultrasound transmission into tissue or MR imaging of the ECD, which in turn can lead to inaccurate treatment or tissue damage. Before use, check that all air bubbles have been removed from the UA and ECD. For instructions on filling devices with water and removing air from the fluid tubing, see 'Fluid Preparation' and 'UA and ECD Preparation' in the TULSA-PRO® Operator's Manual.
Positioning System Setu	The Positioning System (PS) must be set up in accordance with instructions in the TULSA-PRO® Operator's Manual. The PS must be inserted and locked to a customized patient-support base plate, which is firmly attached to the MRI table. The Operator must check that the manual axes are in good working order. Failure to properly set up the PS axes can cause failure of UA translation within the prostate during device positioning and possible patient injury.
Positioning System Automated Axes	UA motion is controlled by automated linear and rotary axes on the Positioning System (PS). Never move these axes manually–use only the motion commands in the software. Manually moving these axes can damage the motors inside the PS.
Handling Portable Components	Take care when handling portable equipment, such as the Positioning System (PS). Damage to equipment can occur if portable equipment is dropped from the height of the MRI patient table
Motion of MRI Table	Ensure that the Positioning System (PS) will not collide with the MRI bore when the patient table is advanced for scanning. Ensure that all cables, tubes, and drapes will not interfere with the motion of the MRI table. Ensure that the patient or Operators will not be pinched or trapped between TULSA-PRO equipment and the moving MRI table. Ensure that the Positioning System (PS) will not collide with the MRI bore
Verifying Equipment Setup	Double-check the integrity of all mechanical fasteners and electrical connectors before operating the TULSA-PRO® System. Faulty connections can cause unpredictable ultrasound delivery during treatment.

Liquid Ingress	The TULSA-PRO® System Electronics (SE) and the Treatment Delivery Console (TDC) are not rated for water exposure. Do not expose the SE or TDC to water or it can cause permanent damage. The System Cart, Positioning System, and Positioning System Interface Box (PSIB) have been tested against and can withstand vertical drops of fluid. Some MRI coils can be permanently damaged when exposed to water: • The TULSA-PRO® coil holder for Philips Achieva and Ingenuity do not protect the MRI coil from liquid ingress; protect the coil holders using absorbing pads or drapes. • TULSA-PRO® coil holders for Siemens Skyra, Siemens Prisma, and Philips Ingenia MRIs do protect the coils from any drops of fluid. • TULSA-PRO® configurations that do not use coil holders and use the MRI spine array will not protect the MRI coil from liquid ingress; protect the spine array using absorbing pads or drapes.  **Always follow the specific IP rating on each piece of equipment for specific water ingress precautions.**
Overturning the System Cart	Do not tilt the TULSA-PRO® System Cart from its upright position. Tilting could cause the cart to overturn and cause injury to the Operator and damage to the equipment.
Contact with TULSA-PRO Equipment	The user must use medical gloves when working with, handling, or positioning the TULSA-PRO equipment
b.ii Therapy Related-Patient Preparation	
Caution	**Description**
Direct Supervision	The use of the TULSA-PRO® System must be prescribed and administered under the direct supervision of a qualified, trained physician and after appropriate medical evaluation of the patient.
Patient MR Screening	Before treatment, the MR technologist must screen the patient for MRI safety, including the MR screening patient questionnaire. This will ensure that the patient is cleared for undergoing an MRI scan and has no medical conditions or implanted medical devices that are contra-indicated for MRI.
Patient Positioning	Take care when positioning the patient on the MRI bed to avoid injury to the patient or equipment damage. To avoid skin burns from electrical currents, do not create any skin-to-skin or skin-to-bore contact when positioning the patient
Coil Positioning	Ensure the MRI coils are positioned so there is adequate signal coverage of the prostate and desired imaging field of view. Ensure the patient is positioned on the recommended area of the coil pad and the anterior MRI coil is placed on top of the patient's pelvis and prostate. Upon initial MR imaging (for example, Localizer), check that there is adequate signal coverage of the prostate and desired imaging field of view; if needed, reposition the anterior MRI coil or patient. Attempting to perform a TULSA treatment with inadequate

	image quality can result in inaccurate temperature measurements and heating of undesired tissue.
Patient Contact with the TULSA-PRO System	The only portions of the system which are intended for patient contact are the UA and the ECD (see Single-use Disposable Devices) All other components are not intended for direct patient contact. Gowns, stockings, sheets, absorbent pads or other patient safe materials should be placed between the patient and the device.
Improper UA Insertion	The UA must be inserted by a trained urologist. Always use a urethral guidewire for inserting the UA, sterile lubricant on the device, and be careful when inserting the UA into the patient's urethra. Perforation and subsequent infection of the urethra can occur if the UA is not placed correctly. To avoid damaging the UA, it must be inserted with the window facing the patient's posterior.
UA Insertion: Poor Coupling	To avoid accidental undertreatment of the prostate tissue due to poor coupling between the UA and prostate, fill the patient's urethra with coupling gel before inserting the UA.
UA Insertion: Urethral Damage	The Ultrasound Applicator (UA) is rigid. The urethra is lined with several thin tissue layers. It is possible to miss the urethral opening and push the UA into the wrong passage between layers, causing patient injury. Possible incorrect insertion issues include: • pushing the UA too far and into the bladder, causing damage • not inserting the UA far enough and rotating the tip within the prostate • pushing the UA tip downwards too much during initial insertion, damaging the urethra, penile bulb, penis, or external urinary sphincter before entering the prostate • locking the UA in a position that applies too much force on the pubic symphysis. Be careful when inserting the UA. Consider using an MR-compatible guidewire to help avoid urethral injury.
Patient Restraint	After the patient is positioned on the MRI bed, restrain the patient's lower torso using a strap to restrict motion during the treatment. Patient motion can cause inaccurate temperature measurements and an inability to monitor heating in the prostate.
Patient Draping or Padding	To avoid electrical shock being passed from components to the patient, place absorbent pads or sheets under the patient to absorb any minor leaks, such as urine. Make sure there is no direct contact between the patient and any external equipment, such as the Positioning System (PS), cables, the bore of the magnet, and MR imaging coils. Sheets, absorbent pads, or other suitable materials should be placed between the patient's skin and the devices.
Gradient Field Hazards	During scanning, gradients produce rapidly changing magnetic fields that can produce peripheral nerve stimulation (PNS) or a tingling sensation in some patients. Ensure that the patient's hands are not clasped or touching, and that feet are not crossed during scanning, which could form a conductive loop

Ear Protection	You must give the patient ear protection before starting scans to help avoid hearing impairment.
Thermal Stress to Patient	The patient might experience warming when exposed to radio frequency electromagnetic fields generated during the MR scan. The MR scanner has an RF power monitor and specific absorption rate (SAR) limitations to help prevent excessive RF exposure to the patient. SAR values are calculated based on the patient's weight. To minimize the possibility of harm, when registering patients for an imaging exam enter their correct weight in the MRI computer software to set operating limits and prevent excessive RF exposure during treatment.
Damaged ECD	The ECD cooling surface can be easily damaged. Be careful when handling the ECD and do not drop it. Never use an ECD that you suspect is damaged. Any cracks or leaks in the ECD could expose the patient's rectal tissue to the ECD Fluid Supplement, which can cause tissue irritation.
Safe Limits for ECD Balloon	When first inflating the ECD balloon, you can safely fill it with between 5-20ml of fluid, followed by small increases with imaging confirmation. The maximum safe limit of ECD balloon inflation is 30ml. For instructions about filling the ECD balloon, see 'Inserting the ECD' in the TULSA-PRO® Operator's Manual.
b.iii Therapy Related-Treatment	
	 It is the responsibility of the treating physician to convey to the patient the relevant potential risks about treatment planning and treatment delivery. When planning for TULSA treatment, the operating physician must balance the aggressiveness of treatment with the desire to spare surrounding anatomy from thermal damage. Structures of concern are on the rectal wall o neurovascular bundles o external sphincter o internal sphincter o pelvic floor muscles. Physicians should be able to identify these structures on MR planning images and follow the TULSA-PRO® Operator's Manual.
Caution	**Description**
Administer Anti-Spasmodic Drug	To eliminate involuntary peristalsis in the patient's rectum, administer a specified dosage of anti-spasmodic drug to the patient before starting treatment planning and again before treatment. Failure to do so can cause motion in the patient anatomy and therefore inaccurate planning or treatment images.
Danger of Ultrasound Power	Only emit ultrasound power when the UA is correctly positioned within the patient's body; otherwise, there could be injury to the patient or Operator.

Verify Correct Treatment Planning Images	Always verify the correct image series is selected for treatment planning. During Detailed Planning in TDC software, always select the most recently acquired AX T2 MR image series for treatment planning. If the patient or any equipment has moved, and the most recent image is not loaded, the treatment plan might not reflect the most current anatomy, and ultrasound could be delivered to unintended tissue.
Verify UA Placemen	Always verify the position of the UA transducer elements within the prostate using MR images through the UA before starting treatment planning. If necessary, adjust the position of the UA to ensure that the ultrasound will not be directed at the external sphincter
Verify ECD Placement	Before treatment planning, always verify the position of the ECD in relation to the prostate using MR images.
Maximum Prostate Radius/Length	The TULSA-PRO® System is not designed to thermally treat regions of the prostate that extend farther than 30mm in any radial direction from the UA center or beyond 50mm in length. Partial gland treatments are possible within these limitations.
Drawing of Thermal Treatment Boundary	It is important that physicians understand and follow the TULSA-PRO® Operator's Manual and only target tissue within the prostate. Reliable temperature measurements cannot be achieved outside of the prostate. Unpredictable thermal damage could result if the Operator tries to target tissue outside of the prostate where temperature measurements are not accurate.
Eliminate air bubbles around UA and ECD	During treatment planning, check the MR images to ensure there are no bubbles in the urethra around the Ultrasound Applicator (UA) and in the rectum around the Endo-rectal Cooling Device (ECD). Bubbles in the rectum can prevent adequate cooling of the rectal tissue by the ECD and affect the accuracy of the thermometry in the surrounding tissue. Bubbles in the path of the ultrasound can cause tissue heating around the bubble and deflect ultrasound to heat tissue outside of the intended treatment volume.
b.iv Therapy Related – Treatment Delivery	
Caution	Description
Treatment Supervision	A physician must always remain at the Operator console and supervise the treatment.
Continuous Monitoring of Treatment Delivery	The system Operator must monitor the user interface continuously during treatment delivery to identify: • movement of the patient during treatment delivery; at any sign of movement, stop treatment • air bubbles in fluid lines that can become lodged in the UA or ECD; at any sign of air bubbles, stop treatment • software warnings related to degradation of image quality, which can affect temperature accuracy • software warnings related to unexpected fluid circuit temperature or pressure • difficulties in achieving enough ultrasound power • misalignment of the ultrasound beam relative to treatment angular position • software warnings related to other equipment malfunctions.

	Failure to monitor and detect these conditions could result in heat delivery and thermal damage to unintended tissue
Boiling of Prostate Tissue	To avoid the risk of boiling prostate tissue and subsequent unpredictable ultrasound absorption in boiled tissue, monitor the temperatures within the control boundary using real-time MR images during treatment delivery. Ultrasound power to the individual elements is shut down if tissue temperature within the target volume in the direction of ultrasound propagation reaches or exceeds 86°C. You will see a warning on the TDC if tissue temperature exceeds 100°C.
Overheating of the UA	If the cooling-fluid circulation is restricted, the transducer elements in the UA can overheat, which can damage the transducer and potentially under-treat the target volume. The pressure of cooling water in the UA line is monitored during treatment. You will see a warning in the indicator section of the TDC if pressure in the UA fluid line becomes unexpectedly too high or too low. If appropriate, the TDC will also interrupt or pause treatment delivery, or prevent treatment from starting, until the UA temperature drops to safe temperatures.
Heating of pelvic floor muscles	Due to variations in patient-specific tissue properties, the rate of heating at the control boundary can in some cases be lower than in the surrounding pelvic floor muscles (levator and obturator). Incidental heating of small portions of the pelvic floor muscles has not resulted in any serious complications and is part of the accepted benefit/risk profile. The physician monitors heating in real-time and can manually pause heating or adjust the treatment plan if required.
b.v Therapy Related – Post Treatment  It is the responsibility of the treating physician to convey to the patient the relevant potential risks about post-treatment care.	
Caution	Description
Never Reuse the UA, ECD, and Fluid Tubing	The TULSA-PRO® System UA, ECD, and tube sets should only be used once and disposed of after treatment, according to the disposal instructions in the TULSA-PRO Operator's Manual. The UA and UA tube set are provided sterile and should not be re-sterilized. Re-sterilization and reuse can cause unsafe treatment or cross contamination between patients.
Disconnecting TULSA-PRO® Components and Cables	Take care when disconnecting cables and components of the TULSA-PRO® System. Extreme force on cables or components can damage equipment. Do not pull AC power cords with extreme force or from a distance greater than 30 cm. If you need to disconnect the System Electronics mains power cord, it is a latching connector, and you must squeeze the two tabs together to remove the cord properly.

Care of Accessories	To prevent permanent damage to TULSA-PRO® System accessories, store, handle, and clean them according to the instructions in this manual and never expose them to temperatures over 50°C during operation.
Improper Cleaning	Insufficient cleaning or use of cleaning methods or agents other than those described in the cleaning instructions can damage equipment or irritate skin for parts in contact with the patient or Operator. Follow the instructions in the corresponding TULSA-PRO Operator's Manual when cleaning reusable components of the TULSA-PRO® System. When cleaning, always use gloves and other personal protective equipment that meet the safety precautions recommended by the manufacturer of the cleaning agents.
Using Supra-pubic Drainage	Always use supra-pubic drainage during and after treatment. Accumulation of urine in the bladder during treatment can cause prostate motion.
Routine Post-Operative Care	It is recommended that a prophylactic antibiotic be administered in accordance with the clinical routines of the department. Also, for the first week after treatment with the TULSAPRO® System, the patient should avoid excessive physical exertion.
Catheterization Period	It is recommended that patients remain catheterized for 1 to 4 weeks. Patients often experience urgency during the first period after treatment. This will reduce gradually, although it is normal for the feeling to persist for up to a month.
Removing the Catheter	You can remove the catheter after a successful voiding trial and at the discretion of the prescribing physician. After removing the catheter, there is still a risk of urine obstruction, retention, or stricture. It is therefore important to tell the patient to seek emergency medical attention if urine retention occurs.
Tissue Sloughing	During the first few months after treatment, it is normal for small pieces of dead tissue or small amounts of blood to be discharged with the urine. This is likely due to the destruction of the prostatic urethra during treatment.
Safety and Effectiveness of Repeat Treatment	he clinical safety and effectiveness of repeat Tulsa-Pro treatments or other salvage procedures and therapies in cases of inadequate treatment or recurrent disease has not been assessed

Appendix B Reference Documents

Document Number	Title / Description
ISO 14971:2019 EN ISO 14971:2019 / A11:2021	Medical devices – Application of risk management to medical devices
ISO/TR 24971:2020	Medical devices – Guidance on the application of ISO 14971
IEC 62304:2015	Medical device software – Software life cycle processes
IEC 60601-1:2005 + A1:2012	Medical electrical equipment – Part 1: General requirements for basic safety and essential performance
IEC 60601-1-6:2010 + A1:2013	Medical electrical equipment - Part 1-6: General requirements for basic safety and essential performance - Collateral standard: Usability
IEC 62366-1:2015	Medical devices - Application of usability engineering to medical devices
IEC 60601-1-8:2006 + A1:2012	Medical electrical equipment - Part 1-8: General requirements for basic safety and essential performance - Collateral Standard: General requirements, tests, and guidance for alarm systems in medical electrical equipment and medical electrical systems
IEC 60601-1-10:2007 + A1:2013	Medical electrical equipment - Part 1-10: General requirements for basic safety and essential performance - Collateral Standard: Requirements for the development of physiologic closed-loop controllers
IEC 60601-2-62:2013	Medical electrical equipment - Part 2-62: Particular requirements for the basic safety and essential performance of high intensity therapeutic ultrasound (HITU) equipment
AAMI TIR34971-2023	Application Of ISO 14971 To Machine Learning in Artificial Intelligence – Guide

Appendix C Results of systematic literature search

Reference	Title
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GCP-10374

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GCP Document • Summary of Safety Clinical Performance (SSCP) for (TULSA-PRO

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