Medical Device Clinical Trial Protocol

Reference Number：U0720

Protocol Title：A real word study to Evaluate the safety and performance of SpaceOAR System when used to create space between the rectum and prostate in men undergoing radiotherapy for localized T1-T2 prostate cancer in China （SpaceOAR System RWS）

Investigational Device	SpaceOAR System SO-2101/10ml
Class of device	Class 3 medical device requiring clinical trials Yes☐ No☒ Same class device within China Yes☐ No☒
Protocol version and date	Ver. A, Oct 12, 2021
Clinical trial sites	Boao Yiling Life Care Center
Principal Investigator	Han Sujun
Sponsor	BSC International Medical Trading (Shanghai) Co., Ltd, (“BSC China”)

A real word study to Evaluate the safety and performance of SpaceOAR System when used to create space between the rectum and prostate in men undergoing radiotherapy for localized T1-T2 prostate cancer in China

SpaceOAR System RWS

U0720

CLINICAL INVESTIGATION PLAN

Sponsored By

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Original Release: Oct 12,2021

Current Version: Oct 12,2021

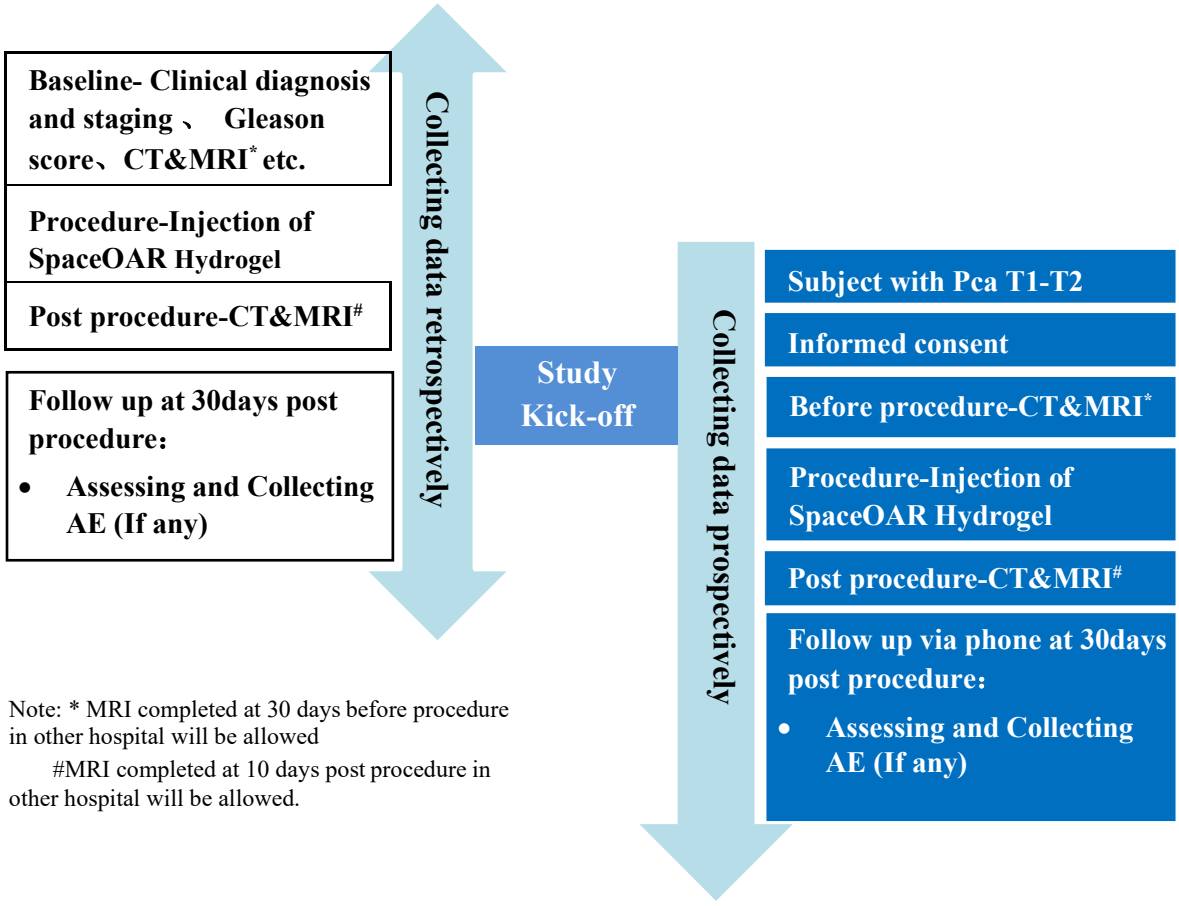
Revision Version	**Protocol Date**	**Template number and version**	**Protocol Section Modified**	**Summary of Changes** [note: confirm with Reg as to level of detail needed (e.g. verbatim or summary)]	**Justification for Modification** [note: Include any potential impact on the performance, effectiveness, safety or other endpoints). Please also update the impacted sections of the protocol as applicable.]
Rev/Ver A	**Oct 12, 2021**	**92129219/ Rev/Ver G**	**NA**	**NA**	**First release**

2. Protocol Synopsis

A real word study to Evaluate the safety and performance of SpaceOAR System when used to create space between the rectum and prostate in men undergoing radiotherapy for localized T1-T2 prostate cancer in China SpaceOAR System RWS	
Study Objective(s)	This study aims to evaluate the safety and performance of SpaceOAR System when it is used to create space between the rectum and prostate in men undergoing radiotherapy for localized T1-T2 prostate cancer in China via collecting the real word data of SpaceOAR System used, to generate local clinical evidence on Chinese patients.
Indication(s) for Use	SpaceOAR System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of SpaceOAR System to reduce the radiation dose delivered to the anterior rectum. The SpaceOAR System is composed of biodegradable material and maintains space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time.
Study Design	This study is a retrospective and prospective, single arm, real world study. For those patients who have already received the SpaceOAR treatment before study kick-off, the data at baseline and the day of procedure will be retrospectively collected. For those patients who will receive SpaceOAR treatment after study kick-off, the clinical data at baseline, the day of procedure and 30 days post procedure will be prospectively collected.

A real word study to Evaluate the safety and performance of SpaceOAR System when used to create space between the rectum and prostate in men undergoing radiotherapy for localized T1-T2 prostate cancer in China

SpaceOAR System RWS



SpaceOAR System RWS Design

Planned Number of Subjects	Up to 20 subjects with a pathologically confirmed diagnosis of clinical stage T1 or T2 prostate cancer indicated for radiotherapy will be enrolled, for there are chances of missing data in the real world study. A sample of 14 subjects provides at least 90% power for the primary objective.
Planned Number of Sites	1 site, Boao Yiling Life Care Center in Hainan BOAO medical tourism pilot zone
Primary Endpoint	**Primary Effectiveness Endpoint**

A real word study to Evaluate the safety and performance of SpaceOAR System when used to create space between the rectum and prostate in men undergoing radiotherapy for localized T1-T2 prostate cancer in China SpaceOAR System RWS	
	The distance between the posterior prostatic capsule and anterior rectal wall post SpaceOAR hydrogel administration. Measurement: The distance between the posterior prostatic capsule and anterior rectal wall is measured on the axial image slice closest to halfway between apex and base, from posterior edge of prostate to inner rectal wall via MRI. **Primary Safety Endpoint** AEs related to SpaceOAR system and/or procedure within 30 days following procedure will be observed.
Secondary Endpoint	Functional Success Defined as creation of at least 7.5mm space between the posterior prostatic capsule and anterior rectum wall as assessed via comparative pre and post SpaceOAR hydrogel injection MRI scans.
Follow-up Schedule	**Retrospective cohort**: For those patients who had been injected with SpaceOAR hydrogel before study kick-off, relevent clinical data at baseline and the day of procedure will be collected retrospectively, any AE at 30 days post procedure will be collected, if applicable. **Prospective cohort:** For those patients who will be injected with SpaceOAR hydrogel, informed consent forms will be gained prospectively, then relevent data will be collected, follow up at 30 days will be conducted to assess any AEs.
Study Duration	The total study duration is estimated to be approximately 3months.
Participant Duration	The study duration for each subject is expected to be approximately 40 days.
Inclusion Criteria	• Subjects has provided the written informed consent, willing to participate in clinical data collection and willing to receive visit at 30 days post procedure. (for subjects enrolled prospectively) • Subjects must have been pathologically confirmed prostate cancer with clinical stage T1-T2, and have been treated or will be treated with Space OAR Hydrogel in hospital in Hainan Boao Lecheng medical pilot zone.

A real word study to Evaluate the safety and performance of SpaceOAR System when used to create space between the rectum and prostate in men undergoing radiotherapy for localized T1-T2 prostate cancer in China SpaceOAR System RWS	
Exclusion Criteria	This is a real world study, all patients who have received or are going to receive SpaceOAR procedure in Boao Medical Pilot Zone will be enrolled in this study. There is no specific exclusion criteria unless the patients refuse to sign the informed consent.
Statistical Methods	
Primary Statistical Hypothesis	This is a retrospective and prospective, single arm study with a performance goal approach for the primary effectiveness endpoint. The primary effectiveness endpoint is the distance between the posterior prostatic capsule and anterior rectal wall post SpaceOAR hydrogel administration. As this is real word study with less strict I/E criteria, the performance goal was set as 7.5mm, based on the rationales in the SpaceOAR EU pilot study, in which the creation of at least a 7.5mm space criterion was developed in consult with Augmenix's Scientific Advisory Board (a panel that consists of board-certified radiation oncologists). If the two-sided 95% Lower Confidence Interval (LCI) of distance calculated is greater than PG, the study primary effectiveness endpoint will be met.
Statistical Test Method	Descriptive statistics will be used to summarize the study endpoints, such as distance between the posterior prostatic capsule and anterior rectal wall post SpaceOAR hydrogel administration, functional success. Continuous variables will be tabulated with mean, median, standard deviation, minimum, maximum. Categorical variables will be tabulated with frequencies, percentages along with the 95% confidence intervals. This study may allow explorative statistics based on collected data, including but not limited to: risk factors associated with functional failure. There is no formal interim analysis, but a descriptive summary will be made during the study, if needed.
Sample Size Parameters	The distance was 12.58±3.88mm (N=147) in the Space OAR hydrogel pivotal study in USA (IDE study), and it was 15.5±5.7mm (N=48) in pilot study in EU. For the sample size estimation, a distance between prostate and rectum of 13 mm is expected with a standard deviation of 5.7 mm. The sample size is calculated according to below formula: $n = \frac{(Z_\alpha + Z_\beta)^2 \sigma^2}{\delta^2}$

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	n is sample size, PG is assumed as 7.5mm, 13mm is expected distance between prostate and rectum, δ = 5.5 mm, σ =5.7 mm, α =0.025, β =0.1（power=90%）. Therefore, a sample size of 14 subjects will provide more than 90% power. To account for potential missing data in this retrospective and prospective study, a final sample size will be up to 20 subjects.

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4. Introduction

4.1. Background

Prostate cancer is one of the most commonly diagnosed noncutaneous human malignancies, and is second only to lung cancer as the leading cause for cancer mortality among men[1]. According to the Surveillance, Epidemiology and End Results Program (SEER) of the NCI, within the United States alone it is anticipated that there will be 233,000 new cases of prostate cancer diagnosed in 2014, with an approximate 29,480 deaths resulting[2]. In China, prostate cancer has became the most common urinary tumor in male since 2008, with a morbidity of 9.8/100,000 and a mortality of 4.22/100,000 in 2014 [3].Gu Xiuying et al. found that the incidence of prostate cancer increased by 11.5% per year on average according China tumor registry data [4].The amount of prostate cancer may increase greatly due to the increase of life expectancy and aging in China.

Reported prostate cancer incidence has increased with introduction of the prostate-specific antigen (PSA) blood test. Application of the PSA test has allowed for earlier detection of prostate cancer and earlier intervention such that disease-specific mortality rates have declined[5]. Treatment options for prostate cancer include surgical resection (radical prostatectomy), radiation (brachytherapy (BT) or external beam radiotherapy (EBRT)), cryotherapy, hormonal therapy (androgen deprivation) or "watchful waiting"/active surveillance involving no immediate treatment but yearly or biannual biopsies or medical monitoring. The choice of treatment is based on a multidisciplinary approach, taking into account tumor staging, Gleason score, baseline PSA, patient age, comorbidity, life expectancy and quality of life. In localized prostate cancer (i.e. T1c-T2c), external radiation therapy is commonly recommended, particularly for young patients who refuse surgical intervention or for patients who are not good surgical candidates[6]. An increasing number of men choose radiotherapy for the treatment of localized prostate cancer because of the perception that there is a lower risk of impotence and incontinence[7].

Although each of the treatment options have associated risks and benefits, one of the more significant concerns associated with radiation therapy (RT) is the potential for acute and late rectal injury caused by direct mucosal damage from ionizing radiation. Since most prostate cancers arise in the peripheral zone (PZ) of the gland including that portion adjacent to the rectum, the radiation oncologist must expose the rectum to high levels of radiation if the tumor is to be effectively treated[8]. However, rectal mucosa has high radio-sensitivity due to rapid cell turnover characteristic of mucosal membranes and, therefore, these tissues are very susceptible to injury resulting in what has been referred to as radiation proctitis. It is for this reason that radiation oncologists refer to the rectum as the dose-limiting structure in prostate cancer radiotherapy.

Acute radiation gastrointestinal (GI) injury is typically characterized as that which occurs during and within the immediate twelve weeks after completion of therapy. Toxicity can be manifested as diarrhea, pain, a sense of rectal distention with cramping, rectal urgency or tenesmus, mucous production and bleeding[9]. Occasionally, superficial ulceration causes bleeding that may require endoscopic cauterization or medical therapy for anemia including transfusion[9,10]. Late effects include rectal dysfunction requiring surgical intervention, necrosis, perforation and life threatening bleeding. Late toxicity is attributable to progressive epithelial atrophy and fibrosis associated with obliterative endarteritis and chronic mucosal

ischemia[11,12]. Symptoms usually are persistent in nature, and may take up to 6-12 months to appear but can occur any time post-irradiation up to 30 years after exposure[11, 13]. Of note, several researchers have documented a positive correlation between acute and late GI toxicity demonstrating that late complications are more likely to occur in patients who also experienced acute complications[9,10,14,15]. Indeed, in an analysis performed by Zelefsky et al. the incidence of late GI toxicity in those patients who experienced acute GI toxicity was substantially and significantly greater than those that had not experienced acute GI toxicity (42% vs. 9% respectively, $p<0.0001$)[16].

There have been several advancements in the delivery of external beam radiotherapy (EBRT) including improvement in accelerator equipment used for the delivery of RT, improved imaging and planning algorithms, and target localization through the use of Image Guided Radiotherapy (IGRT). Despite the improvements in RT delivery, acute and chronic gastrointestinal toxicity remains a concern. With dose-escalation (e.g., ⩾78 Gy), rates of acute and chronic Grade ⩾ 2 rectal toxicity associated with Intensity Modulated Radiation Therapy (IMRT), the most contemporary form of RT, have been documented to range from 3-50% and 5-24%, respectively[16,22].

It is well documented that the volume of normal rectal tissue exposed to varying radiation dose levels represents the most significant factor affecting the development of acute and late rectal toxicity[12,17-21]. Specifically, it has been noted that patients with greater than 25% of the rectum irradiated to 70 Gy had a significantly higher risk of developing Grade 2 or higher rectal toxicity scored using physician reported toxicity RTOG criteria for GI toxicity. Furthermore, all Grade 3 complications occurred when greater than 30% of the rectum received ⩾70 Gy[12]. Other rectal dose metrics have also been qualified as a risk factor for late gastrointestinal symptoms. In particular, for RT prescriptions of 78 Gy or more, higher values for rV40Gy through rV60Gy have been associated with a greater incidence of adverse gastrointestinal reactions, demonstrating the importance of limiting the volume of rectum receiving lower and mid-range doses[23].

Although traditionally GI toxicity has been evaluated based on the physician's assessment, recently there has been a transition to change focus to patient-reported outcomes using detailed quality of life analysis. When evaluating toxicity from a patients' perspective, IMRT has an associated acute and late GI toxicity that has been demonstrated to have an important impact on quality of life[15]. A patient self-assessment questionnaire analysis performed by Koper et al., revealed that soiling and fecal loss (both surrogates for fecal incontinence) and mucus discharge were the most bothering complaints and of greater patient concern than rectal bleeding[24]. In a study published by Sanda et al, radiotherapy was associated with a reduced quality of life related to bowel function early after treatment, and the change lasted for a year or more. Rectal urgency, frequency, pain, fecal incontinence, or hematochezia caused distress related to bowel function in 9% of patients one year after radiotherapy and moderate to severe (i.e., "big") bowel and rectal function was reported in 11% of patients evaluated[25]. These studies lead to the conclusion that non -physician scored toxicity criteria (i.e., parameters not necessarily considered when applying the RTOG toxicity criteria) have a substantial impact on quality of life. Consistent with physician-scored toxicity, increased rectal doses has been demonstrated to have a significant negative impact on patient reported

bowel quality of life (QOL)[26] and early quality of life has been reported to be a strong predictor of later QOL[27].

Based upon the above review, technologies that can minimize rectal exposure to incidental radiation would represent an important tool in modern EBRT therapy. Current technologies that have been employed to attain this goal, as described in the literature, include administration of space-creating absorbable solutions (i.e., hyaluronic acid, collagen and saline) and application of endorectal balloons[28-33]. Ideally, a technique that may have been administered once and be effective throughout the course of radiotherapy treatment would be preferred.

The SpaceOAR System is an in-situ formed absorbable hydrogel that is administered transperineally (with transrectal ultrasound guidance) between the prostate and rectum (posterior to Denonvilliers' fascia and anterior to the fascia propria of the rectum). The formed hydrogel displaces the rectum away from the prostate during prostate radiotherapy and thereby has the potential to reduce rectal wall/mucosa radiation exposure. The SpaceOAR hydrogel material is designed to maintain rectal displacement away from the prostate for three months ensuring a stable relationship between the prostate and rectum during the typical nine week radiotherapy protocol. SpaceOAR hydrogel then slowly absorbs via hydrolysis and is cleared from the implant site in approximately six months.

The SpaceOAR System has been marketed in Australia, Canada, Japan, Europe and USA. A pilot study of SpaceOAR System in Europe enrolled 52 subjects. The objective of the Pilot Study was to evaluate the initial safety and effectiveness of SpaceOAR System when it is injected between the rectum and prostate in adult men undergoing external beam radiation therapy for treatment of low-to-mid risk prostate cancer. The space creation effect of SpaceOAR hydrogel was assessed via co-primary effectiveness endpoints. Analysis of the endpoints for the Per Protocol Population showed that[34], Functional Success, defined as the creation of at least 7.5 mm space between the prostate (Mid-gland) and rectum measured on CT or MRI, was achieved in 46 of 48 subjects (95.8%). Clinical Success, defined as reduction in radiation dose to the anterior rectum as measured by a 25% or greater reduction in rV70 (i.e., the percent volume of the rectum receiving at least 70 Gy) was achieved in 44 of 46 subjects (95.7%). There were no unanticipated adverse events associated with the SpaceOAR System procedure or the SpaceOAR hydrogel. These results from the Pilot Study established initial safety and performance for use of the SpaceOAR System as a means to physically separate the rectum from the prostate and reduce the rectal radiation dose.

The pivotal study of SpaceOAR System in USA aimed to evaluate the safety and effectiveness of the SpaceOAR System when it is used in patients with a pathologically confirmed diagnosis of clinical stage T1 or T2 prostate cancer who were indicated for a course of IMRT. 222 eligible subjects were enrolled and were randomized (2:1) to the Treatment group (SpaceOAR System) or Control group after successful fiducial marker placement. The study showed that hydrogel placement success rate was 99%; Perirectal spaces were 12.6 $\pm$3.9 mm and 1.6 $\pm$ 2.0 mm in the spacer and control groups, respectively. There were no device-related adverse events, rectal perforations, serious bleeding, or infections within either group. The reduction of rectal V70 in treatment group was significantly more than control group (12.4% to 3.3%, P<.0001). Overall acute rectal adverse event rates were similar between groups, with fewer spacer patients experiencing rectal pain.

Late (3-15 months) rectal toxicity were 2.0%,7.0% in treatment group and control group, with a significant reduction and with no late rectal toxicity greater than grade 1 in treatment group[35]. The 3-year incidence of grade ＞1 rectal toxicity were 9.2% , 2.0% in control group and treatment group respectively(P=.028), and the 3-year incidence of grade ＞2 rectal toxicity were 5.7%, 0% in control group and treatment group respectively(P=.012)[36].

4.2. Study Rationale

Prostate cancer occurs mainly in elderly, and occurs rare in men less than 40, the morbidity increase slowly in men more than 40 years old. With the long life expectancy and application of PSA test, the morbidity of prostate cancer increase yearly, the amount of prostate cancar should not be underestimated considering the large population and aging in China. Treatment for prostate cancer varies according to tumor clincal stage,Gleason score etc, external beam radiotherapy is recommended for localized prostate cancer, which long term effectiveness is comparable to surgical resection. Although IGMT could reduce radiation exposure to normal tissues, but damage to the rectum is still inevitable.

The SpaceOAR System is used to displace the rectum away from the prostate during prostate radiotherapy to reduce rectal wall/mucosa radiation exposure, then redurce the rectal damage. This medical device has been marketed in US, Europe and many other countries , and its safety and effectiveness been confirmed in the previous studies in radiotherapy for prostate cancer, it can increase the distance from the rectum to prostate and reduction in radiation dose to the anterior rectum was 25% at least.

The SpaceOAR System is an advanced mecial device, there is no similar device in China. In accordance with the policy on licensed medical devices, SpaceOAR has been applied for clinical use as a licensed medical device in The Boao Lecang Medical Pilot Zone in Hainan.

This study is based on clicnial use of SpaceOAR System in real world, will collect clincial data related to spacerOAR in patients who has been or will be treated with spceOAR retrospectively and prospectively, in order to generate the clinical data in China. This study will evaluate the safety and performance of SpaceOAR Hydrogel System, then support its widespread use in China.

5. Device Description

5.1. Commercial Device Under Study

The SpaceOAR System consists of components for the preparation of a synthetic, absorbable hydrogel spacer and a delivery system package for single use.

The SpaceOAR system is sterile provided, SO-2101/10ml is provided. Components and label are shown in Figure 5-1 , The assembled delivery system prior to needle attachment is shown in Figure 5-2.

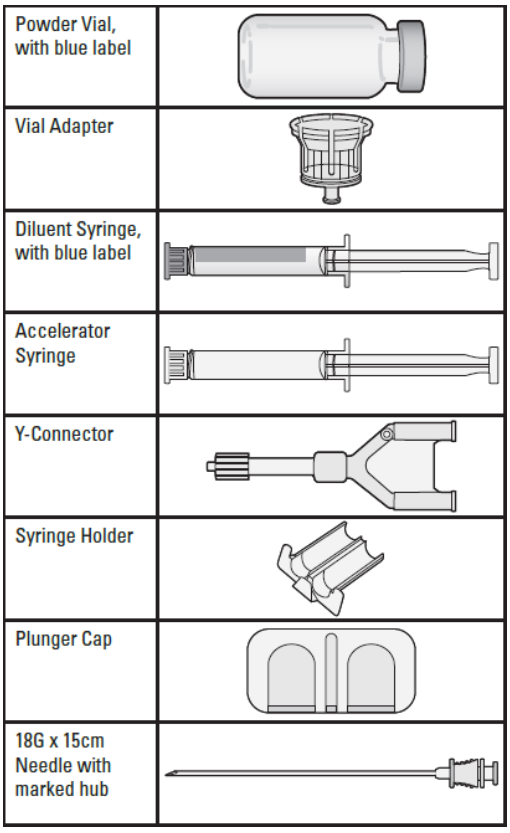

Figure 5-1 SpaceOAR System Components

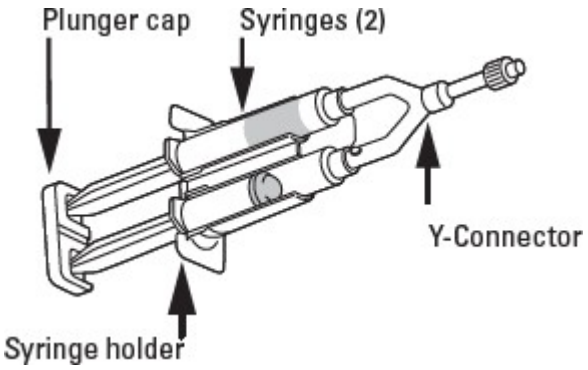

Figure 5-2 SpaceOAR delivery system prior to needle attachment

5.2. Principle of spaceOAR systerm

The SpaceOAR System consists of components for preparation of a synthetic, absorbable hydrogel spacer and a delivery system packaged for single use. The in situ formed hydrogel spacer creates a temporary space between the prostate and rectum during radiation therapy. The spacer is formed by mixing two solutions, the Precursor and the Accelerator. The Precursor solution is formed through the mixing of the Diluent solution (Trilysine buffer solution) with the PEG powder. The Accelerator solution is a salt buffer solution. When mixed together, the solutions cross-link to form a soft hydrogel. The mixing of the solutions is accomplished as the materials pass through a static mixer in the Y-Connector prior to passing through the injection needle. The SpaceOAR hydrogel implant is MR Safe.

The hydrogel spacer maintains space for approximately 3 months and is absorbed in about 6 months, sufficient time to support the intended use.

5.3. Indication(s) for Use

SpaceOAR System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of SpaceOAR System to reduce the radiation dose delivered to the anterior rectum.

The SpaceOAR System is composed of biodegradable material and maintains space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time.

5.4. Required Medical Equipment

For the SpaceOAR System injection procedure, a real time bi-plane transrectal ultrasound (TRUS) and a stepper are required to provide clear, contortion-free images.

5.5. Relevant Medications

The adminstration of prophylactic antibiotics depends on clincial practice in investigation site and the patient's condition, which is at discretion of the doctors.

6. Study Objectives and Endpoints

6.1. Study Objectives

This study aims to evaluate the safety and performance of SpaceOAR System when it is used to create space between the rectum and prostate in men undergoing radiotherapy for localized T1-T2 prostate cancer in China via collecting the real word data of SpaceOAR System used, to generate local clinical evidence on Chinese patients.

6.2. Study endpoints

6.2.1 Primary endpoint

6.2.1.1 Primary effectiveness endpoint

The distance between the posterior prostatic capsule and anterior rectal wall post SpaceOAR hydrogel administration.

Measurement: The distance between the posterior prostatic capsule and anterior rectal wall is measured on the axial image slice closest to halfway between apex and base, from posterior edge of prostate to inner rectal wall via MRI.

6.2.1.2 Primary safety endpoint

AEs related to SpaceOAR system and/or procedure within 30 days following procedure will be observed.

6.2.2 Second endpoints

Functional Success

Defined as creation of at least 7.5mm space between the posterior prostatic capsule and anterior rectum wall as assessed via comparative pre and post SpaceOAR hydrogel injection MRI scans.

7. Study Design

This study is a retrospective and prospective, single arm, real world study. For those patients who have already received the SpaceOAR treatment before study kick-off, the data at baseline and the day of procedure will be retrospectively collected. For those patients who will receive SpaceOAR treatment after study kick-off, the clinical data at baseline, the day of procedure and 30 days post procedure will be prospectively collected.

All administration of SpaceOAR hydrogel will be performed by trained urologists in the hospital in Boao.

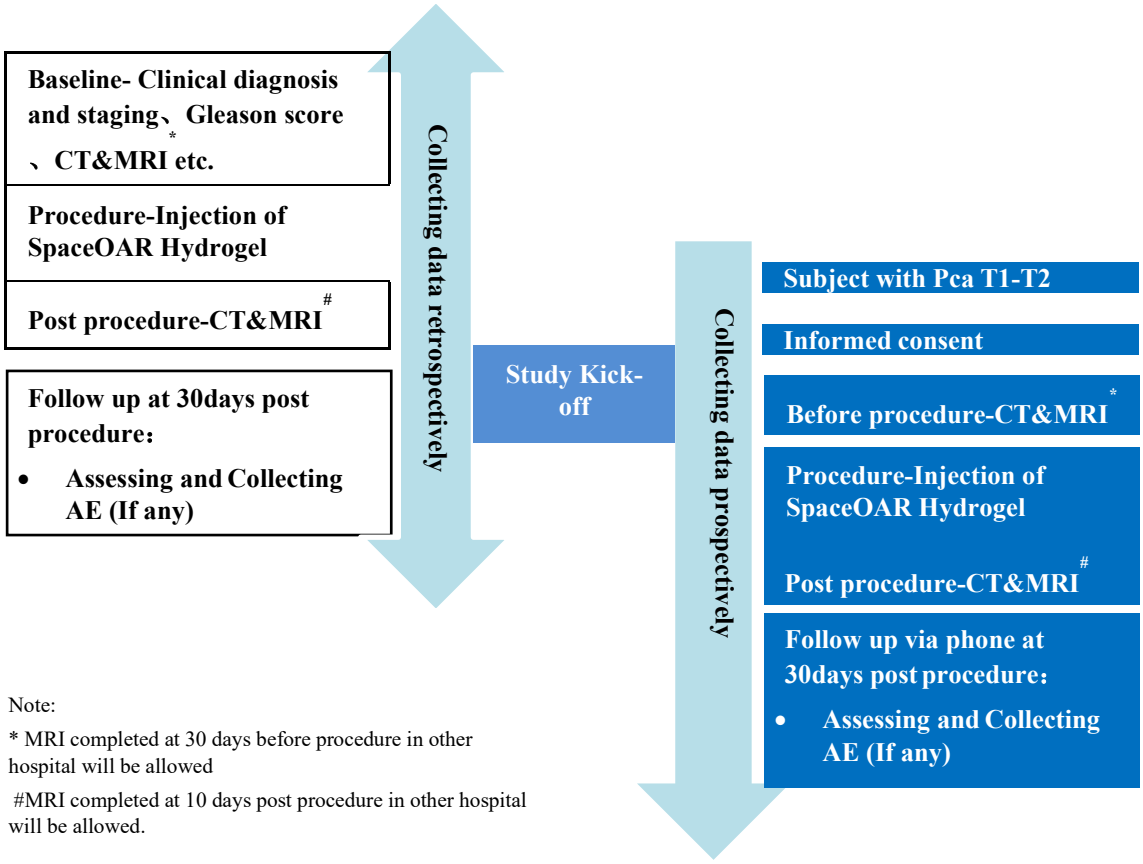

Figure 7-1 SpaceOAR System RWS Design

7.1. Scale and Duration

Up to 20 subjects with a pathologically confirmed diagnosis of clinical stage T1 or T2 prostate cancer indicated for radiotherapy will be enrolled in this study. This study is based on the use of licenced medical device in Hainan BOAO medical tourism pilot zone, the enrollment rate may be slow due to limited patients. The enrollment and 30 days follow up are expected to completed in 3 months.

7.2. Treatment Assignment

This is a single arm study without treatment assignment. All subjects will receive injection of SpaceOAR hydrogel at the hospital in Hainan BOAO medical tourism pilot zone.

7.3. Justification for the Study Design

SpaceOAR system has received CE Mark in 2010 and FDA approval in April 2015 respectively, and it is saled in many countries and regions with good safety and effectiveness. The pivotal study was a randomized control study, which provided a high level of evidence to verify its safety and effectiveness fully. This study aims to generate local clinical evidence on Chinese patients via collecting clincia data related to spacerOAR, which is based on the use of licenced medical device in Hainan BOAO medical tourism pilot zone. Due to limited patient in BOAO, the subjects will be enrolled prospectively and retrospectively, whose data will be collected.

7.4. Method to reduce biases

In order to reduce bias of the measurement of the distance between the posterior prostatic capsule and anterior rectal, MRI before and post procedure are suggested to be completed in same hospital.

8. Subject Selection

8.1. Study Population and Eligibility

The target population are Patients who have been pathologically confirmed prostate cancer with clinical stage T1-T2, and are appropriate for radiotherapy, and have been treated or will be treated with SpaceOAR Hydrogel in hospital in Hainan Boao Lecheng medical pilot zone.

8.2. Inclusion Criteria

Subjects who meet all of the following criteria may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion is met.

- Subjects has provided the written informed consent, willing to participate in clinical data collection and willing to receive visit at 30 days post procedure. (for subjects enrolled prospectively)
- Subjects must have been pathologically confirmed prostate cancer with clinical stage T1-T2, and have been treated or will be treated with Space OAR Hydrogel in hospital in Hainan Boao Lecheng medical pilot zone.

8.3. Exclusion Criteria

This is a real world study, all patients who have received or are going to receive SpaceOAR procedure in Boao Medical Pilot Zone will be enrolled in this study. There is no specific exclusion criteria unless the patients refuse to sign the informed consent.

The indication and health status of subjects are assessed strictly by doctors before use of licenced medical device.

9. Subject Accountability

9.1. Point of Enrollment

For patients who have already received the SpaceOAR treatment, the clinical data can be collected retrospectively when he meets the inclusion criteria and the procedure recored is complete in reviewing medical recoreds. For patients who will receive the SpaceOAR treatment, informed consent will be performed.

9.2. Withdrawal

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study. The applicable CRF, including the study end form, shall be completed by the time of subject withdrawal.(only for patients enrolled porspectively)

9.3. Lost to Follow-Up

A subject will be considered lost to follow-up if he fails to complete 30 days follow-up visits and is unable to be contacted by the study site staff after at least three documented attempts, at which point an End of Study form should be completed. Before a participant is deemed lost to follow up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.(only for patients enrolled porspectively)

9.4. End-of-Study Definition

A subject is considered to have completed the study if he has completed all phases of study including the last visit or last scheduled procedure shown in the data collection schedule.

A clinical trial is considered completed when participants are no longer being examined or the last participant's last study visit has occurred.

9.5. End of Study Action Plan

A subject completes the study when he has receirved spaceOAR treatment and receirved 30 days follow up vist. In light of first use of the spaceOAR in Chinese patients, it is recommended that subjects could participate in the observational study after the injection of spcaceOAR, which is following part of this real word study.

10. Study Methods

10.1. Data Collection

The data collection schedule is shown in table 10-1 .

Table 10-1:Data Collection Schedule

Procedure/Assessment	Before procedure	Procedure	Post pocedure	30 days post procedure（±7days）
Informed conscent#	X			
Demographics	X			
Physical assessment, including weight and height	X			
Clinical diagnosis and clicnial stage of turmor、Gleason score	X			
Medical history（Gerenal disease, genitourinary history / treatment history ）	X			
Questionnaires (IPSS, EPIC, QoL)	X			
Administration of SpaceOAR		X		
PSA	X			
CT&MRI*	X		X	
Concomitant medication		X	X	
Adverse event		X	X	X
Device Deficiency		X	X	X
PD#	X	X	X	X

Note:# only for patients enrolled prospectively；

*MRIs conducted in other hospital are allowed, ie, MRI completed in 30 days before procedure and in 10 days after procedure will be allowed in this study. MRI is required for patients with prostate cancer who recerive radiotherapy; techinial success and distance between the prostate and rectum will beevaluated based on MRI image.

10.2. Study Candidate Screening

After study kick-off, patients who have received treatment of SpaceOAR with a complete procedure recored in hospital in BOAO will be enrolled in this study, who compose retrospective cohort.

For patients who have been confirmed Prostate Cancer with clinical stage T1-T2 and will receive radiotherapy, is scheduled for SpaceOAR administration in hospital in BOAO will be enrolled in this study, who compose prospective cohort.

10.3. Informed Consent

Retrospective cohort: For Patients who have received treatment of SpaceOAR before study kick-off, these relevant clinical data will be collected retrospectively. The study will be conducted according to study procedure approved by EC.

Prospective cohort: For patients who will receive treatment of SpaceOAR, the study will be conducted as usual prospective study, investigator will introduce study information to subject and and get ICF before procedure. Once the ICF is signed, he is considered to be participatie in study. If he fails to receive treatment of spaceOAR after ICF signed, the subjects is considered to be screening failure.

10.4. study visits

10.4.1. Retrospective cohort

For subjects who have received treatment of SpaceOAR, the relevant clincial data below will be collected and be entered in EDC.

- Before procedure: data at baseline will be collect, eg. demographics, physical assessment (height, weight), clinical diagnosis and clinical stage, Gleason score, PSA, CT, MRI and other related examinations, medical history, urinary history and surgery history etc.(Clinical diagnosis and clinical stage, Gleason score, CT and MRI from other hospital wthin 30 days before procedure are allowed, as applicable.)
- Procedure : collecting procedure information such as anesthesia, SpaceOAR dosage, intraoperative device usage, device defects (if any), complications, etc.
- Post procedure: CT and MRI of subjects will be collected retrospectively; Adverse events and device deficiency within 30 days post procedure(if any) will be retrospectively collected.(CT and MRI performed in 10 days after surgery are allowed.)

10.4.2. Prospective cohort

For subjects who have been pathologically confirmed prostate cancer with clinical stage T1-T2, will receive the treatment of spaceOAR in hospital in BOAO. The radiotherapy plan will be made by radiotherapist according to clincial guideline and conditions of subjects.

1) Informed consent

Study objective, schedule and visits will be informed to subjects fully, and the ICF will be signed voluntarily.

2) Before procedure

The data below will be collected, such as demographics, physical assessment (height, weight), clinical diagnosis and clinical stage, Gleason score, PSA, CT, MRI and other related examinations, medical history, urinary history and surgery history etc. IPSS score will be collected, if any, and questionnaires of EPIC and quality of life (EQ-5D-5L) will be completed. (Clinical diagnosis and clinical stage, Gleason score, CT and MRI from other hospital within 30 days before procedure are allowed.)

3) Procedure

According to regulations of licenced medical device in Hainan, subjects will go to BOAO to recerive treatment of SpaceOAR. SpaceOAR is injected between the prostate and rectum via TRUS .

All administration of SpaceOAR hydrogel will be conducted by trained urologists at the hospital in Boao.

Procedure information will be collected, such as anesthesia, SpaceOAR dosage, intraoperative device usage, device defects (if any), adverse events, complications, etc.

4) Post procedure

CT and MRI will be conducted in 10 days post procedure. AE and device deficiency, as applicable, will be assessed. CT and MRI will be conducted for all subjects to complete radiotherapy planning. MRI in other hospital will be allowed to avoid duplication assessment.

5) 30 days follow up vist post procedure

This vists will be conducted vis phone, health status and concommit medication will be inquired, AE and device deficiency (if any) will be assessed and collected.

10.5. Study Completion

This is a real world study on licenced medical device. When last subject complete 30 days (±7 days) follow up visit, and all data is collected, this study will come into end.

10.6. Source Documents

It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

11. Statistical Considerations

11.1. Endpoints

11.1.1. Primary Effectiveness Endpoint

The primary endpoint is The distance between the posterior prostatic capsule and anterior rectal wall post SpaceOAR hydrogel administration.

11.1.1.1. Hypotheses

This is a retrospective and prospective, single arm study with a performance goal approach for the primary effectiveness endpoint. The primary effectiveness endpoint is the distance between the posterior prostatic capsule and anterior rectal wall post SpaceOAR hydrogel administration. As this is real word study with less strict I/E criteria, the performance goal was set as 7.5mm, based on the rationales in the SpaceOAR EU pilot study, in which the creation of at least a 7.5mm space criterion was developed in consult with Augmenix's Scientific Advisory Board (a panel that consists of board-certified radiation oncologists). If the two-sided 95% Lower Confidence Interval (LCI) of distance calculated is greater than PG, the study primary effectiveness endpoint will be met.

11.1.1.2. Sample Size

The distance was 12.58±3.88mm (N=147) in the Space OAR hydrogel pivotal study in USA (IDE study), and it was 15.5±5.7mm (N=48) in pilot study in EU. For the sample size estimation, a distance between prostate and rectum of 13 mm is expected with a standard deviation of 5.7 mm.

The sample size is calculated according to below formula:

$$n = \frac{(Z_\alpha + Z_\beta)^2 \sigma^2}{\delta^2}$$

n is sample size, PG is assumed as 7.5mm, 13mm is expected distance between prostate and rectum, δ = 5.5 mm, σ =5.7 mm, α =0.025, β =0.1（power=90%）. Therefore, a sample size of 14 subjects will provide more than 90% power.

To account for potential missing data in this retrospective and prospective study, a final sample size will be up to 20 subjects.

11.2. General Statistical Methods

11.2.1. Analysis Sets

This study is a retrospective and prospective, real world study, in which subjects who received the treatment of spaceOAR in hospital in BOAO will be enrolled. The efficacy analysis set includes subjects with available distance between prostate and rectum measured from MRI post procedure. The safety analysis set includes all subjects who have received treatment of SpaceOAR in hospitals in Hainan BOA.

11.2.2. Control of Systematic Error/Bias

All patients who receive the treatment of SpaceOAR in hospital in BOAO will be enrolled at a given time, no cherry-pick patinets and data to reduce select bias.

11.2.3. The method of handling missing, incorrect data(including subjects withdrawal and lost to follow-up) and unreasonable data

Missing data will be excluded for primary analysis in this small sample size study. Incorrect and unreasonable data will be clarified before database lock. Imputation where applicable for continuous variable, and tipping point analysis where applicable for categorical variable might be conducted for sensitivity analysis.

11.3. Data Analyses

Descriptive statistics will be used to summarize the study endpoints, such as distance between the posterior prostatic capsule and anterior rectal wall post SpaceOAR hydrogel administration, functional success. Continuous variables will be tabulated with mean, median, standard deviation, minimum, maximum. Categorical variables will be tabulated with frequencies, percentages along with the 95% confidence intervals.

This study may allow explorative statistics based on collected data, including but not limited to: risk factors associated with functional failure.

There is no formal interim analysis, but a descriptive summary will be made during the study, if needed.

Any statistical analysis change will be added in statistical analysis plan before data analysis.

12. Data Management

12.1. Data Collection, Processing, and Review

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by BSC or its representative. The associated Rave software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Medidata EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

All access to the clinical database will be changed to “Read only” after all data is either “Hard Locked” or “Entry Locked”. Once acceptance of the final report or finalization of publications (as applicable) is received, final database storage and archiving activities can begin. Once all of the closeout activities are completed a request to IT is submitted to have the “Database Locked” or Decommissioned and all database access revoked.

12.2. Data Retention

The Principal Investigator or his/her designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements. Documents must be retained for 10 years after the formal discontinuation of the clinical investigation of the product or retained for a long time in accordance with site’s reqiurements . These documents will be retained by BSC until the product/device is no longer in use in compliance with local regulations.

The Principal Investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

13. Amendment

The investigator should adhere to studyprotocol approved by EC. Any Amendment to the protocol (management information or study process modification, etc.) should be completed and reviewed by the sponsor during the study, then should be submitted to the EC for approval via the investigator. Only the amendment of protocol is approved by EC, the amended ptotocol should be implemented.

14. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC, and the regulatory authority if applicable of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using EDC, Sites may also be required to report deviations to the EC, and the regulatory authority, per local guidelines and national/government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including but not limited to EC/regulatory authority notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

Considering that this study is a prospective and retrospective, real world study which is based on the 'pilot program' of licensed medical device, only collecting data, no intervention.

For data retrospectively collected, there is an chance of missing data, so missing data and undo test is not deemed to be deviations.

For prospective enrolled subjects who has signed ICF, Deviations must be recored, including but not limited to informed consent, inclusion criteria, follow-up visit etc.

15. Compliance

15.1. Statement of Compliance

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator.

This study will be conducted in accordance with ISO 14155, ICH-GCP, ethical principles that have their origins in the Declaration of Helsinki, and chinese laws and regulations. The study shall not begin until the required approval/favorable opinion from the EC and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

15.2. Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, the spirit of ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing EC, and prevailing china laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of

interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency. For prospective cohort, investigator will analyze cause of adverse events and write a analysis report with sponsor, then provide suggestion such as continuation, suspension or termination of study according to China GCP. All will be reviewed by EC.
- Report to sponsor, per the protocol requirements, all reportable events.
- Report to the EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain records of the device,which is used in accordance with this protocol and instructions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency

treatment, including decoding procedures for blinded/masked clinical investigations, as needed.

- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided). Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation. All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

15.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, are competent to perform the tasks they have been delegated and adequate supervision of those to whom tasks are delegated. Where there is a sub investigator at a site, the sub investigator should not be delegated the primary supervisory responsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

15.3. Ethics Committee

The investigational site will obtain the written and dated approval/favorable opinion of the EC for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written IRB/EC and/or competent authority (CA) approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor before recruitment of subjects. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. All changes to the ICF will be IRB/EC approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF.
Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/EC requirements. Copies

of the study reports and the IRB/EC continuance of approval must be provided to the sponsor.

15.4. Sponsor Responsibilities

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to Contract Research Organization (CRO), will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

15.4.1. Role of Boston Scientific Representatives

At the request of the investigator and while under investigator supervision, BSC personnel may assist with the conduct of testing specified in the protocol, provide technical expertise.

Typical tasks may include the following:

- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject’s condition or treatment with a subject

- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

15.5. Insurance

Where required by applicable regulation in China, BSC will provide insurance coverage for subjects in the study. If any study related health injury occurs, claims and compensions will be made, where required, and BSC will assume the responsibility per insurance procedure, except in the case that damages are incurred due to deviation of the protocol, intentional or serious negligence at the site.

16. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The source documents include but not limit to signed ICF, mdical recoreds, image(if any), lab tests (if any) and SAEs. The Device deficiencies, relationships of AE and medical device/ procedure recored in the CRF will be considered as souce documents in this study. The sponsor will put a plan in place to document the specific monitoring requirements.

The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities. If the souce docment can’t be acquired for subjects who went to non-investigation hospital or examined by non-investigaor, the certified copies should be got and maintained. Source document related to SAE should be copied (if applicable) and sent to BSC safety,as specified in chapter 18.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

17. Potential Risks and Benefits

17.1. Anticipated Adverse Events and Anticipated Adverse Device Effects

Potential Anticipated adverse events and Anticipated Adverse Device Effects that may be associated with the use of SpaceOAR System include, but are not limited to:

- Pain associated with SpaceOAR hydrogel injection
- Pain or discomfort associated with SpaceOAR hydrogel
- Local inflammatory reactions

- Infection
- Urinary retention
- Mucosal damage, ulcers
- Bleeding
- Constipation
- Urgency(eg urinary and rectal)
- Allergic reaction
- Embolism
- Fistula
- Penetration
- Syncope

17.2. Risks associated with Participation in the Clinical Study

This study is real world study, that the medical data generated in the clinical practice will be used, no new or additional intervention will be imposed on the subjects, no foreseen additional risks. Anticipated Adverse event and risks related to medical device are listed in IFU. During the data collection in the study, no private information that can identify the subject will be collected, such as, name, ID number, hospital number, telephone number, address etc.

17.3. Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

17.4. Anticipated Benefits

There are no guaranteed benefits from participation in this study. However, the data collected from this study will be used to support SpaceOAR to be approved in china, information gained from this study may be of benefit to others with the same medical conditions.

17.5. Risk to Benefit Rationale

The SpaceOAR System is intended to reduce the risk of late Grade 2 or higher GI adverse events. The rate of AEs related to the SpaceOAR System procedure and implant are low. The SpaceOAR System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of the SpaceOAR System to reduce the radiation dose delivered to the anterior rectum.

18. Safety Reporting

18.1. Reportable Events by investigational site to Boston Scientific

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- All adverse events
- All serious adverse events
- All Adverse Events related to Study Device
- All Serious Adverse Events related to Study Device
- All Adverse Events related to the Procedure
- All Serious Adverse Events related to the Procedure
- All Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- New findings/updates in relation to already reported events

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Any reportable event of the subject, whether during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases and chronic conditions are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of one (1) specific SAE (see Table 18-1 for AE definitions).

Refer to Instructions for Use for the known risks associated with the commercial device(s).

18.2. Definitions and Classification

Adverse event definitions are provided in Table 18-1. Administrative edits were made on the safety definitions from applicable regulations and guidance including (but not limited to) 21 CFR Part 812, ISO 14155 and EU MDR 2017/745/MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 18-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the study medical device and whether anticipated or unanticipated. • This includes events related to the study medical device or comparator. • This definition includes events related to the procedures involved. **NOTE** : For users or other persons, this definition is restricted to events related to the study medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of the study medical device • This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. • This definition includes any event resulting from use error or from intentional misuse of the study medical device. • This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) foetal distress, foetal death, or a congenital abnormality or birth defect including physical or mental impairment. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a

Table 18-1: Safety Definitions

Term	Definition
	supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. **NOTE 1**: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2**: This definition includes device deficiencies related to the device under study.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g. medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g. subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g. procedure required by protocol) Note 1: If complications or AEs occur during an elective/planned (i.e., planned prior to signing ICF) hospitalization after signing ICF, the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions, However, the original elective/planned hospitalization(s) itself should not be reported as an SAE.

Table 18-1: Safety Definitions

Term	Definition
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

18.3. Relationship to Study Device(s)(Device Under) and/or Study Procedure

The Investigator must assess the relationship of the reportable AE to the study device(s), and/or study procedure. See criteria in Table 18-2:

Table 18-2: Criteria for Assessing Relationship of Study Device(s) (Device Under Study) or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MDCG 2020-10/1*	Relationship to the device, comparator or procedures can be excluded when: - the event has no temporal relationship with the use of the study device or the procedures related to the use of the study device; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ that cannot be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the study device used for diagnosis, when applicable; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Possibly Related *Ref: MDCG 2020-10/1*	The relationship with the use of the study device or comparator, or the relationship with procedures is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MDCG 2020-10/1*	The relationship with the use of the study device or, comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause.

Table 18-2: Criteria for Assessing Relationship of Study Device(s) (Device Under Study) or Procedure to Adverse Event

Classification	Description
Causal Relationship *Ref: MDCG 2020-10/1*	The serious event is associated with the study device, comparator or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with the study device use/application or procedures; - the event involves a body-site or organ that -the study device or procedures are applied to; -the study device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the study device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

18.4. Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in Table 18-3.

Note: For retrospective cohort, there is no specific reporting requirements for retrospective study in current laws and regulaions. In view of feasibility of operation and specialty of retrospective study, Communication timeline is specified as below.

Table 18-3: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline** (*EU MDR 2017/745, MDCG 2020-10/1*MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• For prospective cohort, within 24 hours of first becoming aware of the event. • For retrospective cohort, within 5 business day of the event identified or collected during data collection • Terminating at the end of the study.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor.
Serious Adverse Event including Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• For prospective cohort, within 24 hours of first becoming aware of the event . • For retrospective cohort, within 5 business day of the event identified or collected during data collection • Reporting required through the end of study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor
Device Deficiencies (including but not limited tomalfunctions, use errors, and inadequacy in information supplied by the manufacturer, including labelling) Note: Any Device Deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, circumstances had been less fortunate is considered a reportable event.	Complete applicable eCRF pagewith all available new and updated information.	• For prospective cohort, within 24 hours of first becoming aware of the event. • For retrospective cohort, within 5 business day of the event identified or collected during data collection • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor

Event Classification	**Communication Method**	**Communication Timeline** (*EU MDR 2017/745, MDCG 2020-10/1*MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner but recommend within 10 business days after becoming aware of the information for retrospective and prospective cohort • Upon request of sponsor
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	

18.5. Device Deficiencies

Device deficiencies will be documented and reported to BSC. If possible, the device(s) under study should be returned to BSC for analysis. The return instructions of the device refer to the return process of the product after market. It shall be returned by the supplier and relevant personnel of the hospital's instrument department. If these device can't be returned, the reason and final deposal will be documented. Device deficiencies and failure to function properly shall also be recorded in the subject's medical record.

Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency, would be recorded as an adverse event on the appropriate eCRF.

18.6. Reporting to Regulatory Authorities ECs / Investigators

BSC is responsible for reporting adverse event information and device deficiency to all participating Principal Investigators, IRBs/ECs and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of UADEs and SAEs as required by China local regulations.

BSC shall notify all participating study centers if SAEs/SADEs or Device Deficiencies occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs demands changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

For the retrospective cohort, BSC shall reprot all SAEs and device deficiencies that may lead to SAE to the regulatory authorities in Shanghai and Hainan within 10 working days within the events identified or collected, and shall notify ECs in a timely manner.

For prospective cohort, BSC shall reprot all SAEs and device deficiencies that may lead to SAE to the regulatory authorities in Shanghai and Hainan within 5 working days upon receipt of such information, and shall notify investigators/investigation site and ECs in a timely manner.

19. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to study-required procedures and/or testing, or data collection in prospective cohort.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's EC, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's EC. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements. Any violations of the informed consent process

must be reported as deviations to the sponsor and local regulatory authorities (e.g. EC, as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the EC. The new version of the ICF must be approved by the EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

20. Committees

20.1. Safety Monitoring Process

The BSC personnel from the Medical Safety and Safety Trial Operation group review safety data as it is reported by the sites throughout the duration of the study. During scheduled monitoring activities, clinical research monitors further support this review through their review of source documents and other data information. The BSC Medical Safety and Safety Trial Operations team include health care providers with expertise in urology and oncology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

20.2. Steering Committee

A Steering Committee composed of the sponsor's Clinical Management and the study Coordinating Principal Investigator(s) may be convened. Responsibilities may include oversight of the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity as well as disseminating any study results through appropriate scientific sessions and publications. Steering Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation, and submission.

There will be no Clinical Events Committee and Data Monitoring Committee in this study.

21. Suspension or Termination

22.1 Premature Termination of the Study

Boston Scientific reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or business reasons and reasons related to protection of subjects. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

22.1.1 Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following:

- Suspicion of an unacceptable risk, including serious health threat. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the EC or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.

22.2 Termination of Study Participation by the Investigator or Withdrawal of EC Approval

Any investigator, or associated EC or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

22.3 Requirements for Documentation and Subject Follow-up

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an EC terminates participation in the study, participating investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents, if supplied by Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

22.4 Criteria for Suspending/Terminating a Study Site

Boston Scientific reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 6 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

The EC and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

22. Study Registration and Results

22.1. Study Registration

To comply with applicable laws and regulations, the study will be registered on a publicly accessible database.

22.2. Clinical Investigation Report

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, EC and regulatory authorities, as applicable in accordance with the Boston Scientific Policy and local requirements. As applicable an abbreviated Clinical Investigation Report will be made available on a publicly accessible database.

22.3. Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC may submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed:

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/en-US/data-sharing-requests.html)

23. Reimbursement and Compensation for Subjects

23.1. Subject Reimbursement

Travel and other expenses incurred by subjects as a result of participation in the study will be reimbursed in accordance with pertinent country laws and regulations and per the study site's regulations.（applicable for subjects with ICF signed for the study）

23.2. Compensation for Subject's Health Injury

Boston Scientific will purchase an insurance policy to cover the cost of potential health injury for study subjects, if required by applicable law.

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25. Abbreviations and Definitions

25.1. Abbreviations

Abbreviations are shown in Table 25-1.

Table 25-1: Abbreviations

Abbreviation/Acronym	Term
ADE	Adverse Device Effect
AE	Adverse Event
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
EBRT	EBRT
eCRF	electronical Case Report Form
EDC	Electronic data capture
FDA	Food and drug administration
GCP	Good clinical practice
Gy	Gy
ICF	Informed consent form
ICH	International Conference on Harmonization
IGRT	Image Guided Radiotherapy
IMRT	Intensity Modulated Radiation Therapy
LCI	Lower Confidence Interval
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
PEG	polyethylene glycol
PSA	Prostate-specific antigen
PZ	Peripheral zone
QoL	Quality of life
RT	Radiation therapy
RTOG	the Radiation Therapy Oncology Group
SAE	Serious adverse event
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect