Medical Device Clinical Trial Protocol

Reference Number：U0745

Protocol Title：An observational study to evaluate the safety and effectiveness of radiotherapy for localized T1-T2 prostate cancer in China after injection of SpaceOAR Hydrogel

(An observational study of radiotherapy after injection of SpaceOAR Hydrogel)

Protocol version and date：	Ver. B, January 25, 2022
Clinical trial sites：	Shanxi Provincial Cancer Hospital
Principal Investigator：	Professor XING Nianzeng
Sponsor:	BSC International Medical Trading (Shanghai) Co., Ltd, ("BSC China")

An observational study to evaluate the safety and effectiveness of radiotherapy for localized T1-T2 prostate cancer in China after injection of SpaceOAR Hydrogel

An observational study of radiotherapy after injection of SpaceOAR Hydrogel

U0745

CLINICAL INVESTIGATION PLAN

Sponsored By

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Original Release: October 28,2021

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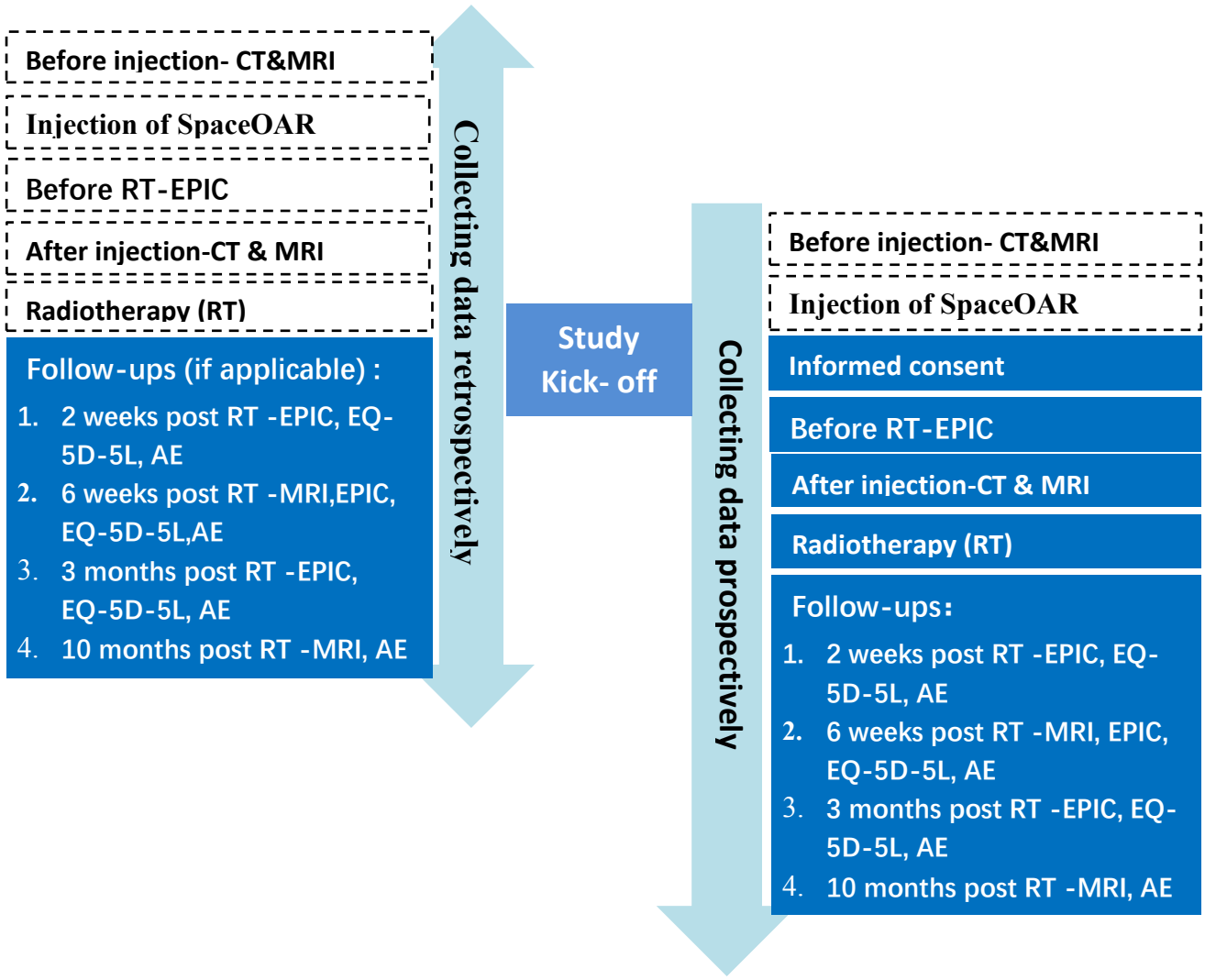
Revision Version	**Protocol Date**	**Template number and version**	**Protocol Section Modified**	**Summary of Changes** [note: confirm with Reg as to level of detail needed (e.g. verbatim or summary)]	**Justification for Modification** [note: Include any potential impact on the performance, effectiveness, safety or other endpoints). Please also update the impacted sections of the protocol as applicable.]
Ver A	Oct 28,2021	92120219_Rev/Ver G	NA	NA	Original release
Ver B	Jan 25,2022	92120219_Rev/Ver G	7.1	Add introduction of "association study-SpaceOAR real world study in Hainan'	Based on EC's opinion
Ver B	Jan 25,2022	92120219_Rev/Ver G	7.2	Add 'The target population in this study are patients diagnosed with localized prostate cancer who took part in SpaceOAR RWS in Hainan (U0720)'.	Based on EC's opinion
Ver B	Jan 25,2022	92120219_Rev/Ver G	9.2	Modified the wording in 'study candidates screening'	Based on EC's opinion
Ver B	Jan 25,2022	92120219_Rev/Ver G	9.4	Add process of SpaceOAR real world study briefly.	Based on EC's opinion
Ver B	Jan 25,2022	92120219_Rev/Ver G	Cover & Contact Information	PI was changed to Professor Xing, and hospital was changed to Shanxi Provincial Cancor hospital	Company Strategy updated

2. Protocol Synopsis

An observational study to evaluate the safety and effectiveness of radiotherapy for localized T1-T2 prostate cancer in China after injection of SpaceOAR Hydrogel An observational study of radiotherapy after injection of SpaceOAR Hydrogel	
Study Objective(s)	This observational study aims to evaluate the safety and effectiveness of radiotherapy for subjects with localized T1-T2 prostate cancer in China who were injected with SpaceOAR Hydrogel, via collecting clinical data related to radiotherapy.
Study design	This study protocol is for the second part of SpaceOAR real world study in which long term follow-up visits will be performed (up to 1 year) outside Boao Medical Tourism Pilot Zone. The SpaceOAR real world study is a retrospective and prospective, single arm, observational study (Ptotocol of SpaceOAR RWS Windchill#: 92743236). Subjects with localized T1-T2 prostate cancer who have already been injected with the SpaceOAR and have received radiotherapy or will receive radiotherapy will be enrolled, and clinical data related to radiotherapy will be collected. For subjects who have already completed radiotherapy before study kick-off, clinical data will be collected retrospectively, such as data related to radiotherapy, AE (if any) and MRI (if any). Follow up vist will be completed if applicable. For subjects who receive therapy after study kick-off, follow up visits at 2 weeks, 6weeks, 3 months and 10 months after radiotherapy will be scheduled to assess bowel, urinary and sexual function and quality of life.

An observational study to evaluate the safety and effectiveness of radiotherapy for localized T1-T2 prostate cancer in China after injection of SpaceOAR Hydrogel

An observational study of radiotherapy after injection of SpaceOAR Hydrogel



Space OAR observational Study Design

Planned Number of Subjects	Up to 20 eligible subjects will be enrolled to generate data including 14 subjects at least.
Planned Number of Sites / Countries	1 site，Shanxi Provincial Cancer Hospital

An observational study to evaluate the safety and effectiveness of radiotherapy for localized T1-T2 prostate cancer in China after injection of SpaceOAR Hydrogel An observational study of radiotherapy after injection of SpaceOAR Hydrogel	
Primary Endpoint	Reduction of dose volume of rectum receiving x Gy as specified below, which is measured from CT simulation scans acquired pre and post SpaceOAR hydrogel injection，that is Vx Gy : • For conventionally fractionated regimen: V70Gy • For moderately hypofractionated regimen: V46Gy, V37Gy • For ultrahypofractionated regimen：V29 Gy, V18. 1 Gy, V36 Gy Dose to the anterior rectum is quantified by computing a rectal dose-volume histogram (DVH).
Second Endpoints	1. EPIC bowel and urinary assessment composite score at 2 weeks, 6 weeks, and 3 months post radiotherapy 2. EPIC sexual assessment composite score at 2 weeks, 6 weeks, and 3 months post radiotherapy 3. Quality of Life at 2 weeks, 6 weeks, and 3 months post radiotherapy (QOL) 4. Whether there is SpaceOAR hydrogel between the posterior prostatic capsule and the anterior rectal wall at 6 weeks post radiotherapy. 5. Whether the SpaceOAR hydrgel between the prostate and the anterior rectal wall is absorbed in 10 months post radiotherapy. 6. Rectal adverse event (CTCAE) 7. AEs/SAEs related to SpaceOAR hydrogel
Follow-up Schedule	Follow ups at 2 weeks, 6 weeks, 3 months, and 10 months after radiotherapy will be scheduled prospectively, if applicable.
Study Duration	The total study duration is estimated to be approximately 15 months.
Participant Duration	The study duration for subject enrolled prospectively is expected to be approximately 12 months.
Inclusion Criteria	• Subjects have provided the written informed consent, are willing to participate in clinical data collection and willing to comply with study procedure. (for subjects enrolled prospectively)

An observational study to evaluate the safety and effectiveness of radiotherapy for localized T1-T2 prostate cancer in China after injection of SpaceOAR Hydrogel An observational study of radiotherapy after injection of SpaceOAR Hydrogel	
	• Subjects must have been pathologically confirmed prostate cancer with clinical stage T1-T2, and have been treated with Space OAR Hydrogel, and have received or will receive radiotherapy.
Exclusion Criteria	This is an observational study, all subjects have received radiotherapy or will receive radiotherapy, who have injected with SpaceOAR hydrogel in Boao Medical Pilot Zone. There is no specific exclusion criteria unless the patients refuse to sign the informed consent.
Statistical Methods	
Statistical Hypothesis	There are no hypotheses for this second stage of the SpaceOAR Real World study. All the endpoints are descriptive in nature.
Statistical Test Method	Descriptive statistics will be used to summarize the study endpoints, which include, but not limited to,dose volume of rectum receiving x Gy, EPIC cpmposite score, and AEs. Continuous variables will be tabulated with mean, median, standard deviation, minimum, maximum, when appropriate. Categorical variables be tabulated with frequencies, percentages along with the 95% confidence intervals when appropriate. There is no formal interim analysis, but a descriptive summary of the study data may be made during the study, if needed.

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4. Introduction

4.1. *Background*

Prostate cancer is one of the most 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 injuries caused by direct mucosal damage from ionizing radiation. 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. Occasionally, superficial ulceration causes bleeding that may require endoscopic cauterization or medical therapy for anemia including transfusion[8,9]. 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[10,11]. 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[10, 12]. 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[8,9,13,14].

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[15,20].

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[11,15-29]. 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[11]. Other rectal dose metrics have also been qualified as a risk factor for late gastrointestinal symptoms.

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[14]. 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[21]. 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[22]. 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)[23] and early quality of life has been reported to be a strong predictor of later QOL[24]. Therefore, technologies that can minimize rectal exposure to incidental radiation would represent an important tool in modern EBRT therapy.

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. It'well documented that the volume of rectum was reduced during radiotherpy when the SpaceOAR System is used as a means to physically separate the rectum from the prostate in previos

studys[25, 26]. The 3 year incidence of grade 1+ and grade 2+ rectal toxicity was reported to reduce significantly when the spaceOAR were used in follow up study (2% vs 9.2%, 0% vs 5.7%)[26].

4.2. *Study Rationale*

The SpaceOAR System is designed to create space between the rcetum and prostate to reduce rectal wall/mucosa radiation exposure during prostate radiotherapy, then reduces the rectal damage. This medical device has been marketed in US, Europe and many other countries, and its safety and effectiveness have been confirmed in the previous studies in radiotherapy for prostate cancer, and Incidence of grade 1+ and grade 2+ rectal toxicity reduced significantly.

The SpaceOAR System is an advanced mecial device, and there is no similar device in China. In accordance with the policy on special innovative medical devices, SpaceOAR can be used in clinical practice as a special innovative medical device in The Boao Lecang Medical Pilot Zone in Hainan. This study will collect relevant clinical data of Chinese patients who received radiotherapy after SpaceOAR hydrogel is administrated, to evaluate its safety and performance during radiotherapy in a real world setting.

5. Study Objectives and Endpoints

5.1. *Study Objectives*

This observational study aims to evaluate the safety and effectiveness of radiotherapy for subjects with localized T1-T2 prostate cancer in China who were injected with SpaceOAR Hydrogel, via collecting clinical data related to radiotherapy.

5.2. *Study endpoints*

5.2.1. Primary endpoint

Reduction of dose volume of rectum receiving x Gy as specified below, which is measured from CT simulation scans acquired pre and post SpaceOAR hydrogel injection(i.e.Vx Gy):

- For conventionally fractionated regimen: V70Gy
- For moderately hypofractionated regimen: V46Gy, V37Gy
- For ultrahypofractionated regimen：V29 Gy, V18. 1 Gy, V36 Gy

Dose to the anterior rectum is quantified by computing a rectal dose-volume histogram (DVH).

5.2.2. Second endpoints

1. EPIC bowel and urinary Assessment composite score at 2 weeks, 6 weeks and 3 months post radiotherapy

2. EPIC Sexual Assessment composite score at 2 weeks, 6 weeks, and 3 months post radiotherapy
3. Quality of Life at 2 weeks, 6 weeks and 3 months post radiotherapy (QOL)
4. Whether there is SpaceOAR hydrogel between the posterior prostatic capsule and the anterior rectal wall at 6 weeks post radiotherapy.
5. Whether the SpaceOAR hydrgel between the prostate and the anterior rectal wall is absorbed in 10 months post radiotherapy.
6. Rectal adverse event (CTCAE)
7. AEs/SAEs related to SpaceOAR hydrogel

6. Study Design

The SpaceOAR real world study is a retrospective and prospective, single arm study, and this study protocol is for the second part of the SpaceOAR real world study in which long term follow-up will be performed (up to 1 year) outside Boao Medical Tourism Pilot Zone. Subjects with localized T1-T2 prostate cancer who have already been injected with the SpaceOAR and have received radiotherapy or will receive radiotherapy will be enrolled, and clinical data related to radiotherapy will be collected.

For subjects who have already completed radiotherapy before study kick-off, clinical data will be collected retrospectively, such as data related to radiotherapy, AE (if any) and MRI (if any), and follow up will be performed, if applicable.

For subjects who receive therapy after study kick-off, radiotherapy relevant clinical data will be collected, and follow up visits after radiotherapy will be scheduled to assess urinary, bowel, sexual functions and AE.

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

All radiotherapy planning will be made according to clinical practice and stage of Pca at discretion of the doctors.

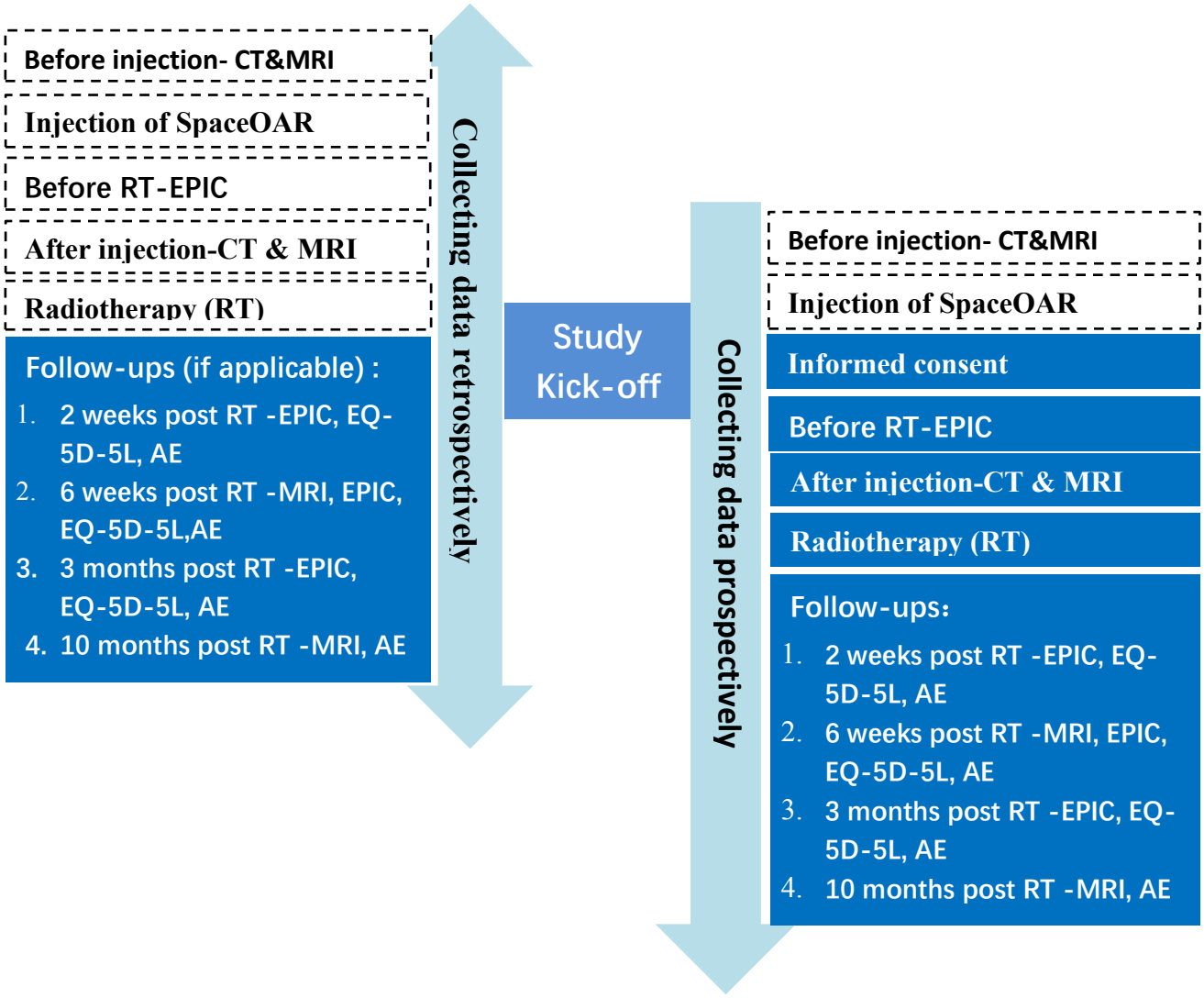

Figure 6-1 Space OAR observational Study Design

6.1. *Scale and Duration*

Up to 20 subjects with localized Pca will be enrolled in this study and followed by radiotherapy after injection of SpaceOAR. This study is based on the use of special medical device in Hainan BOAO medical tourism pilot zone, the enrollment may be slow due to limited patient pool. Together, the study enrollment, radiotherapy, and follow up visits are expected to be completed in 15 months.

6.2. *Treatment Assignment*

This is a single arm, observational study without treatment assignment. All subjects receive radiotherapy in sites when they were treated with SpaceOAR hydrogel at the hospital in Hainan BOAO.

6.3. *Justification for the Study Design*

SpaceOAR system has been firstly used in Hainan BOAO as a special medical device, while there is no evidence about the radiotherapy after SpaceOAR hydrogel injection in China. As a result, an observational study is conducted to gather the relevant clinical data in Chinese patients with localized PCa who receive radiotherapy after SpaceOAR hydrogel is injected. Due to limited patient pool in BOAO, the subjects will be enrolled prospectively and retrospectively to speed up the study recruitment..

6.4. *Method to reduce biases*

To reduce bias of primary endpoints, objective endpoints, Vx Gy, are used. They are obtained by computing a rectal dose-volume histogram (DVH) in the same hospital.

7. Subject Selection

7.1. *Association study-SpaceOAR Real World Study in Hainan（U0720）*

SpaceOAR Real World Study is conducted based on the use of special medical devices in the Boao Lecheng Medical Pilot Zone in Hainan. Patients who have been diagnosed with stage T1-T2 prostate cancer and are scheduled to receive radiation therapy will be recommended to participate in the SpaceOAR RWS after informed consent is done fully. If patients voluntarily participate in the study, they can go Boao Yiling Life Care Center in Hainan to receive SpaceOAR gel injection.

The injection of SpaceOAR hydrogel is performed by trained urologists, via rectal ultrasound guided under general anesthesia or local anesthesia and sedation. Subjects will go back Local hospital, where simulated mapping CT and MRI examination will be performed to make radiotherapy treatment plan in time post-discharge (Shanxi Provincial Cancer Hospital is recommended).

Subjects will be called by phone at 30 days after discharge to collect adverse events and Device Deficiency (if applicable) to assess patient health. The relevant clinical data generated in another hospital (e.g., Local hospital where subjects have been examined) will be collected when applicable.

In addition, the study will retrospectively collect the clinical data of patients who had completed SpaceOAR hydrogel injection before the study kick-off.

7.2. *Study Population and Eligibility*

The target population in this study are patients diagnosed with localized prostate cancer who took part in SpaceOAR RWS in Hainan (U0720) and have been treated with SpaceOAR Hydrogel in hospital in Hainan Boao, are receive or will receive radiotherapy in this site.

7.3. *Inclusion Criteria*

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

- Subjects have provided the written informed consent, are willing to participate in clinical data collection and willing to comply with study procedure. (for subjects enrolled prospectively)
- Subjects must have been pathologically confirmed prostate cancer with clinical stage T1-T2, and have been treated with Space OAR Hydrogel, and have received or will receive radiotherapy.

7.4. *Exclusion Criteria*

There are no specific exclusion criteria unless the patients refuse to sign the informed consent.

8. Subject Accountability

8.1. *Point of Enrollment*

During screening, patients who have received or will receive radiotherapy will be identified. These who have been injected with SpaceOAR hydrogel will be enrolled. For patients who have already received radiotherapy, the clinical data can be collected retrospectively, and informed consent will be performed (If follow up visits can be conducted prospectively). For patients who will receive radiotherapy, informed consent will be gained.

8.2. *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. The applicable CRF(s), including the end of the study form, shall be completed at the time of subject withdrawal.

8.3. *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 prospectively).

8.4. *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. Study Methods

9.1. *Data Collection*

The data collection schedule is shown in Table 9-1.

Table 9-1: Data Collection Schedule

Procedure/Assessment	Before RT	RT	After RT			
			2W (± 3days)	6W (± 7days)	3M (± 15days)	10M (± 30 days)
Informed consent	X					
PSA	X			X		X
CT	X*					
MRI	X*			X		X
Radiotherapy		X				
EPIC questionnaire	X		X	X	X	
EQ-5D-5L questionnaire	X		X	X	X	
Concomitant medication	X	X	X	X	X	X
Adverse event	X	X	X	X	X	X
Protocol Deviation	X	X	X	X	X	X
Device Deficiency#	X	X	X	X	X	X

NOTE:1. Data at baseline such as demography, medical history, Pca, etc. refer to SpaceOAR RWS (U0720).
2.*CT&MRI for mapping, which used to make RT planning, 2 times.
3.# DD of Space OAR hydrogel.

9.2. *Study Candidate Screening*

Patients diagnosed with localized prostate cancer who have been injected with SpaceOAR hydrogel in SpaceOAR RWS in Hainan (U0720) will be invited to participate in this study.

9.3. *Informed Consent*

For patients who receive radiotherapy after SpaceOAR injected, investigator will introduce study information to subject and get ICF. Once the ICF is signed, he is enrolled in study. If he fails to receive radiotherapy after ICF signed, the subjects are screening failure.

9.4. *study visits*

The subject of SpaceOAR RWS are going to participate in this study when he completed last visit. the process of SpaceOAR RWS is summarized below.

- Patients who diagnosed with T1-T2 prostate cancer and scheduled to recerive RT will be screened and recommended to participate in SpaceOAR RWS in Hainan. After informed consent is done fully, Mapping CT and MRI will be conducted. (Shanxi Provincial Cancer Hospital is preferred.)
- Subjects go to Boao Yiling Life Care Center in Hainan to receive SpaceOAR gel injection voluntarily, which is completed by trained and qualified urologist.
- After discharge, subjects will recerive Mapping CT and MRI to make RT plan, then recerive RT. (Shanxi Provincial Cancer Hospital is preferred, i.e., enrolled in this study)
- At 30 days after SpaceOAR injection, a phone visit will be completed. Then subject complete all visits.

Subjects who have been injected with SpaceOAR in Hainan BOAO return to participate in this observational study. subjects receive radiotherapy per site's clinical practice, then will be followed in 2 weeks, 6 weeks, 3 months and 10 month after RT.

1) Before RT

   RT planning before and after SpaceOAR hydrogel injection will be made (such as planning type of EBRT, planning RT regimen, CTV, PTV and constraint of risk organs, etc.). The RT planning of the subjects will be determined by the investigators based on the current clinical practice and PCa staging and conditions of the subjects.

   The questionaries of EPIC and EQ-5D-5L will be completed, adverse event and Device Deficiency (if applicable) will be assessed and collected.

   Note: The subject's demographic, medical history, genitourinary history, prostate treatment, PCa therapies, PCa staging, Gleason score, etc., are collected in the SpaceOAR RWS(U0720).

2) RT

   RT is conducted according to RT planning after SpaceOAR injection; adverse event and Device Deficiency will be collected, if applicable.

3) Follow-ups after RT

   2 weeks post RT: the questionaries of EPIC and EQ-5D-5L will be completed to assess the functions of urinary, rectum and health related Quality of life; Adverse event and Device Deficiency will be collected, if applicable.

   6 weeks post RT: the questionaries of EPIC and EQ-5D-5L will be completed to assess the functions of urinary, rectum and health related Quality of life; Adverse event and Device Deficiency will be collected, if applicable; MRI will be performed.

3 months post RT: the questionaries of EPIC and EQ-5D-5L will be completed to assess the functions of urinary, rectum and health related Quality of life; Adverse event and Device Deficiency will be collected, if applicable.

10 months post RT: MRI will be performed; Adverse event and Device Deficiency will be collected, if applicable.

NOTE: For subjects who have received RT (after SpaceOAR injection), applicable follow up will be performed after participation in this study to assess adverse event and device deficiency, if any, then to collect clinical data. The clinical data before participation will be collected retrospectively at same time.

9.5. *Study Completion*

When last subject complete follow up visit at 10 months post RT and data collection is complete, this study will come to an end.

9.6. *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.

10. Statistical Considerations

10.1. *Study hypotheses*

There are no hypotheses for this second stage of SpaceOAR Real World study. All the endpoints are descriptive in nature. The endpoints in the study include the following:

Primary endpoint

Reduction of dose volume of rectum receiving x Gy as specified below, which is measured from CT simulation scans acquired pre and post SpaceOAR hydrogel injection, (i.e.Vx Gy):

- For conventionally fractionated regimen: V70Gy
- For moderately hypofractionated regimen: V46Gy, V37Gy
- For ultrahypofractionated regimen：V29 Gy, V18. 1 Gy, V36 Gy

Dose to the anterior rectum is quantified by computing a rectal dose-volume histogram (DVH).

Secondary endpoints

1. EPIC bowel and urinary assessment composite score at 2 weeks, 6 weeks, and 3 months post radiotherapy
2. EPIC sexual assessment composite score at 2 weeks, 6 weeks, and 3 months post radiotherapy
3. Quality of Life at 2 weeks, 6 weeks, and 3 months post radiotherapy (QOL)
4. Whether there is SpaceOAR hydrogel between the posterior prostatic capsule and the anterior rectal wall at 6 weeks post radiotherapy.
5. Whether the SpaceOAR hydrgel between the prostate and the anterior rectal wall is absorbed in 10 months post radiotherapy.
6. Rectal adverse event (CTCAE)
7. AEs/SAEs related to SpaceOAR hydrogel

10.2. *General Statistical Methods*

10.2.1. Analysis Sets

The effectiveness set, and safety set include all subjects who have radiotherapy after injection of SpaceOAR hydrogel.

10.2.2. Control of Systematic Error/Bias

All patients who receive RT at the BOAO site after injection of SpaceOAR will be invited to enroll at a given time, to minimize selection bias. The primary endpoint is an objective measure, which is computed via DVH to reduce assessment bias.

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

Missing data will not be imputed for primary analysis. Incorrect and unreasonable data will be clarified before database lock. Imputation with mean or median may be performed where applicable for the primary endpoint as a sensitivity analysis.

10.3. *Data Analyses*

Descriptive statistics will be used to summarize the study endpoints, such dose volume of rectum receiving x Gy, EPIC composite score, AEs. 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 when appropriate.
Any statistical analysis changes for the study endpoints will be described in the statistical analysis plan before the data analysis.

11. Data Management

11.1. *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 the sponsor 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 may 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.

11.2. *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.

12. Amendment

The investigator should adhere to clinical trial protocol 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.

13. 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 IRB/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 IRB/EC, regulatory authority notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

Since this study is a prospective and retrospective, real world study without intervention based on standard medical care, missing data and tests are not deemed as study deviations for the restrospectively collected data. For prospectively collected data, deviations should be recorded, including but not limited to informed consent, inclusion criteria, follow-up visit etc.

14. Compliance

14.1. *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 applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/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 IRB/EC or regulatory authority shall be followed, if appropriate.

14.2. *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 IRB/EC, and prevailing local and/or country 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 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 an 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 IRB/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 IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- 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 IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/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.
- 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.

14.2.1. 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.

14.3. *Institutional Review Board/ Ethics Committee*

The investigational site will obtain the written and dated approval/favorable opinion of the IRB/EC for the clinical investigation before recruiting subjects.

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 into the. 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.

14.4. *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.

14.4.1. Role of Boston Scientific Representatives

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

14.5. *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 compensation 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.

15. 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, medical records, image (if any), lab tests (if any) and SAEs. The Device deficiencies, relationships of AE and medical device/ procedure recorded in the CRF will be considered as source 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 source document can't be acquired for subjects who went to non-investigation hospital or examined by non-investigator, 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 17.

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.

16. Potential Risks and Benefits

16.1. *Anticipated Adverse Events and Anticipated Adverse Device Effects of SpaceOAR system*

All subjects were treated with SpaceOAR system, which were implanted between prostate and anterior rectum before participation in this study. It slowly absorbs via hydrolysis and is cleared from the implant site in approximately six months. Anticipated adverse events and Anticipated Adverse Device Effects of SpaceOAR system are specified as below:

- 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 (e.g., urinary and rectal)
- Allergic reaction
- Embolism
- Fistula
- Penetration
- Syncope

16.2. *Risks associated with Participation in the Clinical Study*

This study is an observational 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. But the risks of PCa and treatment may not be reduced when subjects take part in this study. 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.

16.3. *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 follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

16.4. *Anticipated Benefits*

There are no guaranteed benefits from participation in this study. However, information gained from this study may be of benefit to others with the same medical conditions.

17. Safety Reporting

17.1. *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 RT
- All Serious Adverse Events related to RT
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- All Device Deficiencies
- 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 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, experienced by the study subject after informed consent, whether prior to, during or after RT, 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 investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of one (1) specific SAE (see Table 17-1 for AE definitions).

17.2. *Definitions and Classification*

Adverse event definitions are provided inTable 17-1. 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 17-1: 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.

Table 17-1: Safety Definitions

Term	Definition
	• 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 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)	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment.

Table 17-1: Safety Definitions

Term	Definition
Ref: ISO 14155 *Ref: MDCG 2020-10/1*	**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.
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.

Table 17-1: Safety Definitions

Term	Definition

17.3. *Relationship to Study Device(s) (Device Under Study and Comparator Device, if applicable) and/or Study Procedure*

The Investigator must assess the relationship of the reportable AE to SpaceOAR hydrogel, and/or radiotherapy. See criteria in Table 17-2:

Table 17-2: Criteria for Assessing Relationship of Study Device or RT to Adverse Event

Classification	Description
Not Related *Ref: MDCG 2020-10/1*	Relationship to the device, comparator or RT can be excluded when: - the event has no temporal relationship with the use of the study device or the RT - 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/RT or the reduction of the level of activation/exposure/RT - 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 RT; - 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/RT 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/RT and the serious event.
Possibly Related *Ref: MDCG 2020-10/1*	The relationship with the use of the study device or RT, or the relationship with RT 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, or the relationship with RT seems relevant and/or the event cannot be reasonably explained by another cause.
Causal Relationship *Ref: MDCG 2020-10/1*	The serious event is associated with the study device or with RT beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and RT; - the event has a temporal relationship with the study device use/application or RT; - the event involves a body-site or organ that -the study device or RT are applied to; -the study device or RT 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.

17.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 17-3.

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

Table 17-3: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (*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 data collected prospectively: within 24 hours of first becoming aware of the event. • For data collected retrospectively, 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 effects	Complete AE eCRF page with all available new and updated information.	• For data collected prospectively: within 24 hours of first becoming aware of the event. • For data collected retrospectively, 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 to malfunctions, use errors, and inadequacy in information supplied by the manufacturer, including labelling) Note: Any Device Deficiency that might have led to a	Complete eCRF page with all available new and updated information.	• For data collected prospectively: within 24 hours of first becoming aware of the event. • For data collected retrospectively, within 5 business day of the event identified or collected during data collection • Reporting required through the end of the study

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (*EU MDR 2017/745, MDCG 2020-10/1*MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
serious adverse event if appropriate action had not been taken, intervention had not occurred, circumstances had been less fortunate is considered a reportable event.	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor
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 • Upon request of sponsor
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	

17.5. *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.

17.6. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

BSC is responsible for reporting adverse event information 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 Chinese 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 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 data collection retrospectively, BSC shall report 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 during data collecting.

For data collection prospectively, BSC shall report 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.

18. Informed Consent

Subject participation in this clinical study is voluntary. The Investigator is responsible for ensuring that Informed Consent is obtained prior to study-required procedures and/or testing, or data collection for subjects enrolled prospectively. For subjects enrolled retrospectively, informed consent process of the protocol specified approved by EC will be followed.

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 IRB/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 IRB/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 IRB/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. IRB/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 IRB/EC. The new version of the ICF must be approved by the IRB/EC/REB. 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.

19. Committees

19.1. *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, Radiation Oncology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

19.2. *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 are no Clinical Events Committee and Data Monitoring Committee in this study.

20. Suspension or Termination

20.1. *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 IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

20.1.1. 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 IRB/EC/REB or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.

20.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval*

Any investigator, or associated IRB/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 IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

20.3. *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

IRB/EC/REB 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 IRB/EC terminates participation in the study, participating investigators, associated IRBs/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 and devices, if supplied by Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

20.4. *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.

In the event of termination of site participation, The IRB/EC and regulatory authorities, as applicable, will be notified. Study participants will be contacted and followed, as applicable.

21. Study Registration and Results

21.1. *Study Registration*

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

21.2. *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, IRB/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.

21.3. *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)

22. Reimbursement and Compensation for Subjects

22.1. *Subject Reimbursement*

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

22.2. *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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24. Abbreviations and Definitions

24.1. *Abbreviations*

Abbreviations are shown inTable 24-1.

Table 24-1: Abbreviations

Abbreviation/Acronym	Term
ADE	Adverse Device Effect
AE	Adverse Event
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
DVH	Dose Volume Histogram
EBRT	External beam radiation therapy
eCRF	electronical Case Report Form
EDC	Electronic data capture
EPIC	The Expanded Prostate Cancer Index Composite
FDA	Food and drug administration
GCP	Good clinical practice
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
QoL	Quality of life
RT	Radiation therapy
CTCAE	Common Terminology Criteria for Adverse Events
SAE	Serious adverse event
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect