Statistical Analysis Plan

A real world 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）

Study Reference # U0720

APPROVALS (Check/Complete one below):

☒ Approvals are captured electronically

☐ An electronic system for capturing approvals is not being used for this study; wet signatures are captured below:

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Revision History

Document Revision Date	Version	Section	Change	Reason for Change
18Jan2023	Ver: A	NA	Initial Release	

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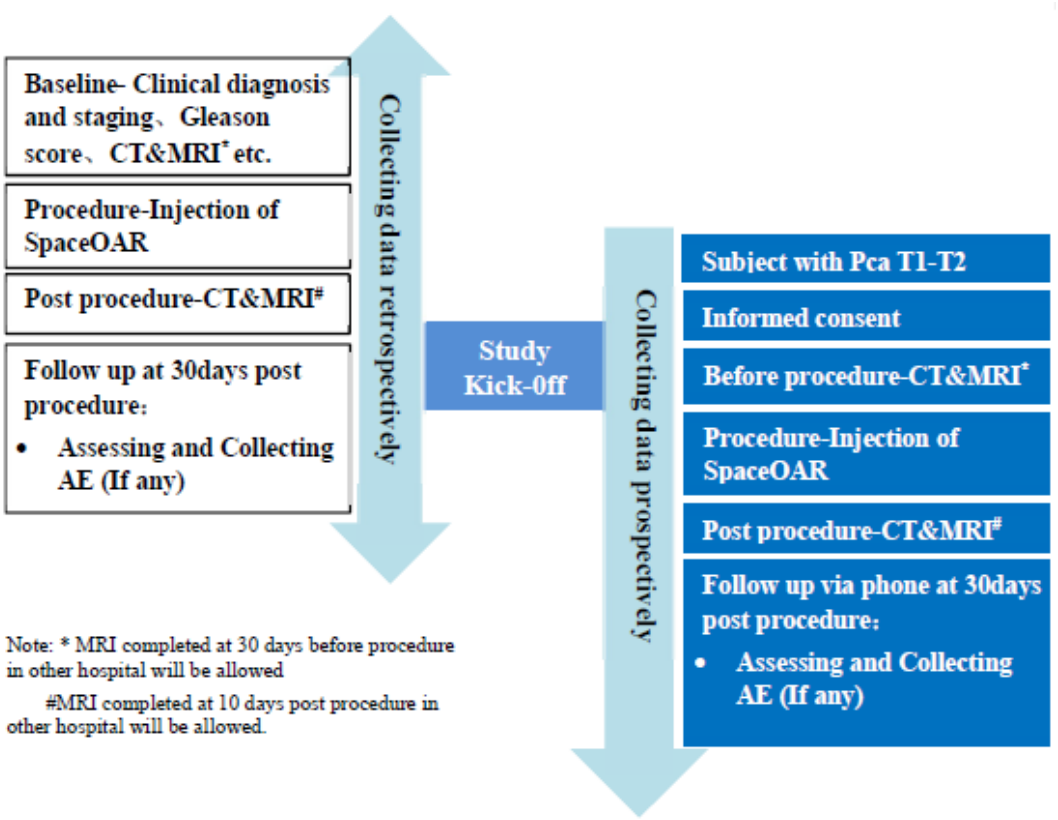
1 PROTOCOL SUMMARY

1.1 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.



SpaceOAR System RWS Study Design

1.2 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 world data of SpaceOAR System used, to generate local clinical evidence on Chinese patients.

1.3 Number of sites and patients

The study will be conducted at a site in the Boao Yiling Life Care Center in Hainan BOAO medical tourism pilot zone. 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.

1.4 Description of the study population

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.

1.5 Description of device

The SpaceOAR System consists of components for the preparation of a synthetic, absorbable hydrogel spacer and a delivery mechanism provided in a sterile, single use package. The SpaceOAR hydrogel is a synthetic, absorbable polyethylene glycol (PEG)-based hydrogel that upon injection creates a space that temporarily positions the anterior rectal wall away from the prostate during radiotherapy for prostate cancer, and in creating this space it is the intent of the perirectal spacer to reduce the radiation dose delivered to the anterior rectum.

The hydrogel is formed by mixing together two solutions, the Precursor and Accelerator. The Precursor is a solution containing Diluent solution(trilysine) and PEG-power dissolved. The Accelerator is an aqueous solution containing phosphate and borate buffer salts. When mixed together using the assembled delivery system, the solutions cross link to form an absorbable hydrogel. The hydrogel is compatible with MRI.

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.

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.

The administration of prophylactic antibiotics depends on clinical practice in investigator and the patient's condition, which is at discretion of the doctors.

1.6 Follow-up schedule

Retrospective cohort: For those patients who had been injected with SpaceOAR hydrogel before study kick-off, relevant clinical data at baseline and 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 formed will be gained prospectively, follow up at 30 days will be conducted to assess any AEs.

The data collection schedule is shown in below table:

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.

1.7 Study duration

The total study duration is estimated to be approximately 3 months. The expected study duration for each subject is approximately 40 days.

1.8 Key Inclusion Criteria

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

- Subjects have provided the written informed consent, are 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.

1.9 Key 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 licensed medical device.

2 INTRODUCTION

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. In China, prostate cancer has become 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. Prostate cancer occurs mainly in elderly, and rare in person younger than 40, the morbidity increases slowly in person over 40 years old. The occurrence rate of prostate cancer may increase greatly due to the increased life expectancy and aging in China. Treatment for prostate cancer varies according to tumor clinical stage, and Gleason score etc. External beam radiotherapy is recommended for localized prostate cancer, with long term efficacy comparable to surgical resection. Although IGMT could reduce radiation exposure to normal tissues, 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, thus reduce 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 has shown that the distance from the rectum to prostate and reduction in radiation dose to the anterior rectum was increased by at least 25%.

The SpaceOAR System is an advanced medical device, and there is no similar device in China. This study collects real world clinical data related to SpaceOAR System in patients who has been or will be treated with SpaceOAR retrospectively and prospectively, in order to generate the clinical data in China. This study will evaluate the safety and performance of SpaceOAR Hydrogel System to support its widespread use in China. All safety parameters and additional endpoints will also be analyzed. These analyses are detailed in the endpoint analysis section below.

3 ENDPOINT ANALYSIS

3.1 Primary Safety/Effectiveness Endpoints

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.

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

3.1.1 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 world study with less strict I/E criteria, the performance goal was set as 7.5mm. The choice of this performance criterion is based on the rationales that for the SpaceOAR EU pilot study, a creation of at least a 7.5mm space was considered clinical meaningful in the consultation 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.

3.1.2 Sample Size

The sample size for effectiveness endpoint was estimated based on the following assumptions:

- Confidence level $(1-\alpha) = 0.975$
- Expected distance between prostate and rectum: 13 mm
- Estimated standard deviation: 5.7 mm
- Power: 90%

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 the expected distance between prostate and rectum, $\delta = 5.5$ mm, $\sigma = 5.7$ mm, $\alpha = 0.025$, $\beta = 0.1$ (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.

3.1.3 Statistical Methods

Descriptive statistics (mean, median, SD, min and max) along with corresponding 95% confidence interval will be used to summarize the effectiveness endpoints, such as distance between the posterior prostatic capsule and anterior rectal wall post SpaceOAR hydrogel administration. One sample t-test will be used to calculate the p-value for

primary effectiveness endpoint. To summarize safety endpoint, AEs related to SpaceOAR system and/or procedure within 30 days 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.

3.2 Secondary 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 diagnostic quality MRI scans.

3.2.1 Hypothesis

No formal tests of hypotheses are proposed for secondary endpoints. No formal inferences are planned on the additional assessments.

3.2.2 Statistical Methods

The proportion of subjects who experiences a functional success will be summarized along with the 95% confidence interval (Clopper-Pearson Exact Method).

4 GENERAL STATISTICAL METHODS

4.1 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 measurement 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 BOAO.

All enrolled set: Retrospective subjects, who have already received the SpaceOAR treatment, are enrolled when they meet the inclusion criteria. Prospective subjects, who will receive the SpaceOAR treatment, informed consent will be performed for enrollment.

4.2 Control of Systematic Error/Bias

All patients who receive the treatment of SpaceOAR in hospital in BOAO will be enrolled during the study period to minimize selection bias.

4.3 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 with mean or median where applicable for continuous variable, and tipping point analysis where applicable for categorical variable might be conducted for sensitivity analysis. Visit-wise mean and LOCF imputation methods will be used for missing values.

Missing Event Dates Considerations:
For adverse events with missing event date (i.e., mm/dd/yyyy), the safety and/or data management representatives will query sites for missing data. In the event that the date for adverse event is missing at the time of analysis, please reference Section 7.4 for the missing/partial date handling rules.

5 ADDITIONAL DATA ANALYSES

5.1 Interim Analyses

There is no planned formal interim analysis. A descriptive summary may be made during the study, if needed.

5.2 Other Analyses

5.2.1 Baseline Data Analyses

Subject demographics, medical history, EQ-5D-5L, Extended Prostate Cancer Index Composite (EPIC), Prostate Cancer Staging and Gleason score will be summarized using descriptive statistics. For continuous variables, the descriptive statistics will include mean, standard deviation, minimum and maximum. For discrete variables, frequency tables will be displayed. No formal statistical testing will be performed.

5.2.2 Procedure Analyses

Procedure information such as anesthesia, SpaceOAR dosage, intraoperative device usage, device defects, complications, etc. will be summarized using descriptive statistics for continuous and frequency with percentages for discrete variables. No formal statistical testing will be performed.

5.2.3 Post-procedure Analyses

Post-procedure information will be collected at 30 days and will be summarized using descriptive statistics for continuous and frequency tables or proportions for discrete variables. No formal statistical testing will be performed.

5.2.4 Patient disposition/status

Subject Disposition of follow-up Compliance will be provided at Post-procedure, 30days post procedure visit. A listing for deaths will be provided with relatedness to study device and study procedure, with date of death and duration of days from index procedure date.

5.2.5 Analysis of Adverse and Serious Adverse Events

Frequency of site reported Serious adverse events and Non-serious adverse events associated with the study device will be summarized. The events will be summarized by MedDRA system organ class and MedDRA system preferred terms with event counts and proportions. A listing based on all site reported adverse events with seriousness, relationships and duration days will be created. Similarly, a listing for all anticipated/un-anticipated adverse device events with seriousness and duration from onset date will be also produced.

For calculating events and rates, 'Events numbers' are total number of episodes for each type of event among all subjects. 'Rate of Subjects with Event' numbers are percent of subjects who experienced one or more episodes of the event. 'Events' numbers for "TOTAL" are the sum of the individual event category totals. 'Rate of Subjects with Event' numbers for "TOTAL" is the percent of subjects who experienced at least one adverse event.

5.2.6 Protocol Deviations

Deviations from Investigational Protocol collated during procedure and post procedure for all the planned events as specified in protocol will be captured and summarized. A table summarized with counts and percent and another summary table presented based on deviations reasons will be presented. A listing will be provided with deviation type, reason, visit and assessment/procedure requirement during the study for all subjects.

5.2.7 Device Deficiencies

A table will be produced for device deficiencies with count and percent by deficient components. A supported listing will be provided by subject, and if its leading to any event.

5.3 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the primary endpoint analysis will be documented in an amended Statistical Analysis Plan which will be approved prior to performing the analysis. Changes from the planned statistical methods after performing the analysis will be documented in the clinical study report along with a reason for the deviation.

6 VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation. The validation level R1 chosen for all primary,

secondary, safety and other additional endpoints. The validation program includes checking logs and generating compare reports in comparing with main programming datasets. Statistical analyses and validation will be performed by IQVIA team.

7 PROGRAMMING CONSIDERATIONS

All statistical programming tasks will be performed by IQVIA™ independently.

7.1. Statistical Software

All statistical analyses will be done using The SAS System Version 9.2 software or above (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved.).

7.2. Format of Output

Statistical analysis will be performed using SAS. All output for the final statistical report will be in the form of a Word document, which may include tables, figures, graphs, and listings, as appropriate.

7.3. Rules and Definitions

For baseline categorical variables, subjects with missing values will not be counted in the corresponding denominators for proportions. Number of patients completing the visit will be considered in denominators.

7.4. Handling of Missing/Partial Date

Missed or late visits will be recorded as Protocol Deviations.

When calculating rates of all adverse events, both device and/or procedure related with missing event date (i.e. mm/dd/yyyy), every effort should be made to work with safety and/or data management representatives to query sites for missing data. However, in the situations when it cannot be resolved, missing and partial missing dates may be handled as using the worst-case scenario as follows:

Partial Date Description	Action taken
Entire onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1st will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.