Statistical Analysis Plan

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 Reference # U0745

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
16APR2024	Ver: A	NA	Initial Release	

Abbreviation

Abbreviation	Description
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	Electronic 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
SAP	Statistical Analysis Plan
SD	Standard Deviation
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect

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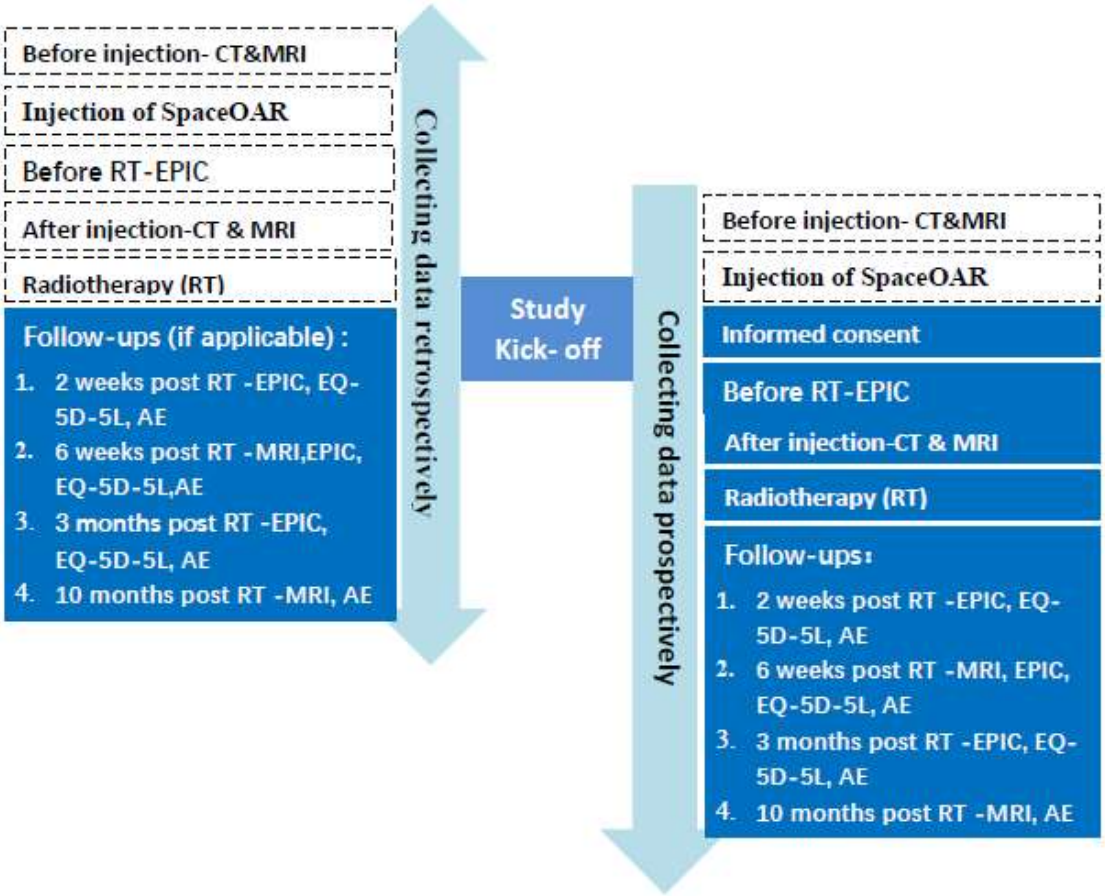
1 PROTOCOL SUMMARY

1.1 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 (Protocol 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 visit 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.



Space OAR observational Study Design

1.2 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.

1.3 Number of sites and patients

The study will be conducted at a site in the Shanxi Provincial Cancer Hospital. Up to 20 eligible subjects will be enrolled to generate data including 14 subjects at least.

1.4 Description of the study population

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

1.5 Study Rationale

The SpaceOAR System is designed to create space between the rectum 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 medical device, and there is no similar device in China. In accordance with the policy on licensed medical devices, SpaceOAR can be used in clinical practice as a licensed 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.

1.6 Follow-up schedule

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

- 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).

- RT

Radiotherapy will be conducted per planning RT; adverse event and Device Deficiency will be collected, if applicable.

- 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.

The data collection schedule is shown in below table:

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

Procedure/Assessment	Before RT	RT	After RT			
			2W (± 3days)	6W (± 7days)	3M (± 15days)	10M (± 30 days)
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.						

1.7 Study duration

The total study duration is estimated to be approximately 15 months. The study duration for subject enrolled prospectively is expected to be approximately 12 months.

1.8 Key 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.

1.9 Key Exclusion Criteria

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

2 INTRODUCTION

The Statistical Analysis Plan (SAP) is based on SpaceOAR Observation-China protocol version B and the electronic case report form (eCRF) version 5.0. It documents the planned analysis outlined in the protocol, and is consistent with the study objective. Specified analyses may be used for scientific presentations and/or manuscripts, and regulatory submissions. This is an observational study to evaluate the safety and effectiveness of radiotherapy for localized T1-T2 prostate cancer in China after injection of SpaceOAR Hydrogel. This study protocol is for the second part of SpaceOAR real world study.

SpaceOAR system has been firstly used in Hainan BOAO as a licensed 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.

3 ENDPOINT ANALYSIS

3.1 Primary Endpoints

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).

3.1.1 Hypothesis

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

3.1.2 Sample Size

No formal sample size calculation is performed. The study plans to enroll up to 14 subjects.
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

For continuous and ordinal variables, descriptive statistics will include number of observations, mean, standard deviation, minimum and maximum. Specific variables may also include additional statistics such as median, interquartile range (IQR) and confidence intervals. For binary or categorical variables, descriptive statistics will include percentage, numerator, denominator and number of missing observations if applicable. When the distribution of a variable does not support the use of parametric statistics, nonparametric approaches may be implemented. A parametric method of paired t-test or wilcoxon signed-rank non parametric test will be used for before and after clinical assessments.

3.2 Secondary Endpoints

- EPIC bowel and urinary assessment composite score at 2 weeks, 6 weeks, and 3 months post radiotherapy.
- EPIC sexual assessment composite score at 2 weeks, 6 weeks, and 3 months post radiotherapy.
- Quality of Life at 2 weeks, 6 weeks, and 3 months post radiotherapy (QOL).

- Whether there is SpaceOAR hydrogel between the posterior prostatic capsule and the anterior rectal wall at 6 weeks post radiotherapy.
- Whether the SpaceOAR hydrgel between the prostate and the anterior rectal wall is absorbed in 10 months post radiotherapy.
- Rectal adverse event (CTCAE).
- AEs/SAEs related to SpaceOAR hydrogel.

3.2.1 Hypothesis

No formal tests of hypotheses are proposed for secondary endpoints.

3.2.2 Statistical Methods

For continuous and ordinal variables, descriptive statistics will include number of observations, mean, standard deviation, minimum and maximum. Specific variables may also include additional statistics such as median, interquartile range (IQR) and confidence intervals. For binary or categorical variables, descriptive statistics will include percentage, numerator, denominator and number of missing observations if applicable. When the distribution of a variable does not support the use of parametric statistics, nonparametric approaches may be implemented. A parametric method of paired t-test or wilcoxon signed-rank non parametric test will be used for before and after clinical assessments.

4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

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

4.2 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.

4.3 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. 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 formal interim analysis, but a descriptive summary of the study data 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), PSA, CT and MRI 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 Post-procedure Analyses

Post-procedure information will be collected at 2 weeks, 6 weeks, 3 months and 10 months. And they will be summarized using descriptive statistics for continuous and frequency tables or proportions for discrete variables. No formal statistical testing will be performed.

5.2.3 Patient disposition/status

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

5.2.4 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.

5.2.5 Protocol Deviations

Deviations from Investigational Protocol collected 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.

5.2.6 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.