Protocol Signature Page

Tracking Renal Tumors After Cryoablation Evaluation (TRACE)

Protocol Number CUC10-RNL02-03
Study Design Registry
Date 20 May 2011

Galil Protocol Approval

We, the undersigned, have read and approve the protocol specified above and agree on its content.

Maria Plentl, MSN
Director, Clinical Research

Maria Plentl
Signature

Amy McKinney
Director, Regulatory Affairs

Amy E. McKinney
Signature

Investigator Signature

I, the undersigned, have read and understand the protocol specified above and agree on its content. I agree to perform and conduct the registry as described in the protocol.

Printed Name	Signature	Date

Protocol Title:	Tracking Renal Tumors After Cryoablation Evaluation (TRACE)
Sponsor:	Galil Medical 4364 Round Lake Rd. Arden Hills, MN 55112
Registry Responsibility:	Maria Plentl, MSN Director, Clinical Research Galil Medical 4364 Round Lake Rd. Arden Hills, MN 55112
Date of Issue:	20 May 2011
Protocol Number:	CUC10-RNL02-03

This protocol contains confidential information for use by the Investigators and their designated representatives participating in this Registry. It should be held confidential and maintained in a secure location.

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Protocol Synopsis

Tracking Renal Tumors After Cryoablation Evaluation (TRACE)

Protocol Number	CUC10-RNL02-03
Objectives	The primary objective of the study is to assess the short- and long-term outcomes of subjects who undergo renal lesion ablation via cryotherapy with products offered by Galil Medical. Secondary objectives are: • An assessment of outcomes across laparoscopic-assisted, percutaneous and open cryoablation procedures • Characterization of standards of care for cryoablation procedure follow-up across the participating registry centers
Registry Design	An observational, open-label, single-arm, multi-center study of subjects who have undergone renal lesion cryoablation per their physician's standard of care
Registry Device	The study will include subjects who have undergone cryoablation via a Galil Medical cryoablation system using Galil Medical needles
Control Device	Not applicable
Number of Sites	Approximately 10 sites in the United States are anticipated to participate; a mix of academic and community centers
Number of Subjects	Approximately 250 subjects are anticipated to be enrolled
Registry Methodology	Patients with a renal lesion suspicious for malignancy pre-operatively who have been determined to be an appropriate candidate for cryoablation will be offered enrollment into the registry. Patients agreeing to participate will read and sign an informed consent form. Participation in the registry will not influence direct subject treatment procedures or follow-up care schedule. Each physician will manage their enrolled subjects as per their individual standard of care and provide data regarding each subject as they are seen. Baseline and follow-up data will be collected for each subject via a web-based electronic data collection tool.
Randomization	Not applicable

Procedural Measures	Cryosurgery parameters will include: • Procedure method (open, laparoscopic, percutaneous) • Number of lesions treated with cryoablation • Type of hemostatic agents or maneuvers used • Lesion size • Lesion location • Number and type of cryosurgery needles used • Number of freeze and thaw cycles • Freeze and thaw times, per cycle • Hilar clamping • Embolization • Galil needle cautery • Method of thaw (active or passive) • Method of monitoring iceball formation (US, CT, MRI) • Involvement of the kidney's collecting system • Post-operative HCT
Safety Measures	Primary safety parameters will include: • Evaluation of cryosurgery-related adverse events
Outcome Measures	Outcome parameters will include: • Changes in lesion size • Renal function status as determined by estimated Glomerular Filtration Rate • Length of hospital stay • Post-cryoablation lesion enhancement • Post-cryoablation biopsy (if performed) • Disease recurrence or progression • Disease-specific survival rates • Overall survival rates and times • Quality of Life assessment • Emergence of new neoplastic disease (any type) • Development of metastatic disease
Follow-Up Schedule	Planned per-subject follow-up is 5 years

Inclusion Criteria	1. Patient is at least 18 years of age. 2. Renal lesion suspicious for malignancy. 3. Patient is to undergo renal lesion cryoablation via a Galil Medical cryoablation system using Galil Medical needles for treatment of primary or recurrent disease. 4. Patient is to be available for long-term follow-up per the enrolling physician's standard care practices. 5. Patient has provided written informed consent.
Key Exclusion Criteria	1. Patient is either currently using or has used within the last 30 days an investigational product of any type. 2. Patient has metastatic disease to or from the kidney. 3. Patient has had previous therapy on the index lesion (e.g. radiofrequency, cryoablation, partial nephrectomy).
Renal Lesion Size Criteria	While there are no strict exclusion criteria with regard to lesion size, the typical renal lesion suitable for cryoablation is ≤ 4 cm. Physicians are to use their training and experience to determine the size of a renal lesion that is appropriate for cryoablation.
Statistical Methods	Continuous variables (e.g., age) will be summarized by the number of subjects, mean, standard deviation, median, minimum and maximum. Categorical variables (e.g., race) will be summarized by frequencies and percentages of subjects in each category. Reporting from the database will include: • Baseline demographics and disease status will be summarized. • Disease recurrence or progression will be summarized. • Survival and disease-specific survival rates will be summarized at given time points. • Overall survival (time to death) disease-specific survival (time to death of kidney cancer), and recurrence free survival (time to disease recurrence or progression) will be analyzed using the Kaplan-Meier methodology and presented graphically. • Follow-up patterns across physicians/centers will be summarized. • Lesion size reduction will be analyzed. • Relative efficacy in subject subgroups may be explored.

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1. Background

1.1. Cryotherapy

Cryosurgery is a safe, well-established FDA-cleared technology that has been successfully applied for selective ablation and treatment of different kinds of benign and malignant conditions, such as: prostate and renal cancer, liver lesions, soft tissue lesions, fibroadenoma of breast, ear-nose and throat applications, thoracic applications (atrial fibrillation, pulmonary lesions), cryoanalgesia, dermatology, as well as pre-cancerous lesions of the cervix. Galil Medical has developed a range of products based on its cryotherapy platform and incorporating updated freezing technology and needle design. The company's core technology is a significant advance in cryoablative treatment of renal and other lesions.

1.2. *Cryo-Technology*

Modern cryoablation dates back to 1961, when automated cryosurgical units that pump liquid nitrogen through the tip of the cryoprobe were introduced.[1] This innovation led to the investigation of cryoablation for different diseases, but cumbersome cryoprobes and a lack of control over the freezing process made widespread use impractical. The resurgence in interest in cryoablation results from the introduction of modern cryoprobes, which exploit the Joule–Thomson (J–T) effect.[2] The J–T effect predicts changes in temperature as gases expand through narrow ports from high to low pressure. This is a constant enthalpy expansion that, in the case of argon gas, results in rapid cooling to the boiling point of argon (-186°C). To accomplish this, high-pressure (3,000 psi) ambient-temperature argon gas is circulated to the cryoprobe tip where it expands rapidly as it drops to room pressure. Under the J–T effect, some gases - such as helium - warm up rather than cool when expanded. Accordingly, helium can and has been incorporated into cryogenic systems to rapidly warm the cryoprobe in order to arrest the freezing process or thaw the iceball. The flow of argon and helium is controlled by computer-modulated gas regulators. The temperatures of cryoprobes controlled by gas systems are finely adjustable and respond within seconds to user input. (By comparison, liquid nitrogen systems have a lag time of up to 2 minutes.) [3,4] The expanded gases are circulated back to the cryogenic unit through the larger outer lumen of the cryoprobe and the supply hose. The venting of used gas, usually into the room, occurs at the cryogenic machine. Both argon and helium are inert gases, making such venting harmless.

2. Device Description

2.1. Cryotherapy Systems

The cryo-technology developed by Galil Medical, Ltd. (Yokneam, Israel) is based on Joule-Thomson effect, and utilizes Argon gas for freezing. Passive thaw, helium gas thaw or electric thaw may be used.

This registry will utilize Galil Medical's commercially available needles and thermal sensors. Each cryogenic needle forms a different shape and size of iceball. Multiple cryogenic needles can be operated simultaneously. Thus, insertion of several cryogenic needles into the lesion, or even into 2 or 3 lesions concomitantly significantly shortens the length of treatment, and provides flexibility in treating lesions of varying sizes by matching the cryoablation needle number and configuration for a specific lesion. Tissue thermal sensors enable the real-time tissue temperature monitoring, thus contribute to the safety and effectiveness of the procedure.

Galil Medical's commercially available cryotherapy systems and associated needles are FDA cleared for use as a cryosurgical tool in the fields of general surgery, dermatology, neurology (including cryoanalgesia), thoracic surgery, ear-nose and throat (ENT), gynecology, oncology, proctology and urology. These systems are designed to destroy tissue (including prostate and kidney tissue, liver metastases, tumors, skin lesions and warts) by the application of extremely cold temperatures. Cryoablation procedures using Galil's systems may be performed under the guidance of ultrasound, CT or MRI. During the last eight years, thousands of cryoablation procedures have been safely and effectively performed with Galil's cryoablation equipment, primarily for the treatment of prostate and kidney cancers, as well other applications.

3. Registry Rationale

The data generated by the registry database will evaluate the use, safety and effectiveness of cryotherapy for renal lesions and will assess the potential advantages and disadvantages of the procedure (e.g., disease recurrence or progression, disease-specific survival rates, overall survival rates, etc.). It will also be used to facilitate long-term surveillance of subjects undergoing renal lesion cryoablation. In addition, the registry may be used as a continuous quality improvement tool on behalf of the treating physicians and will contribute to the development and refinement of standards of care.

4. Registry Objectives

The primary objective of the registry is to assess the short- and long-term outcomes of subjects who undergo renal lesion ablation via cryotherapy with products offered by Galil Medical.
Secondary objectives are:

- An assessment of outcomes across laparoscopic-assisted, percutaneous and open cryoablation procedures.
- Characterization of standards of care for cryoablation procedure follow-up across the participating registry centers.

5. Registry Design

5.1. Description of the Registry

TRACE is an observational, open-label, single-arm, multi-center registry of subjects who have undergone renal lesion cryoablation per their physician's standard of care. Patients 18 years of age or older who have been determined to be an appropriate candidate for cryoablation will be offered enrollment into the registry. Subjects will be recruited from a variety of practice settings, including academic centers and community-based physicians. Those agreeing to participate in the registry will read and sign an informed consent form prior to their cryoablation procedure. Subjects will be observed for five years from the date of their cryoablation procedure.

The registry is non-interventional; it will neither direct the cryoablation procedures performed nor define the post-surgery follow-up of each subject. A subject's participation in the registry will not influence or direct subject treatment procedures or follow-up care. Physicians will use their discretion and personal standards of care to select subjects, perform the cryoablation procedures and define appropriate follow-up visit schedules for their subjects; it is anticipated that subjects will be seen at least once per year during the five-year follow-up period of TRACE. Subjects may be followed by the physician performing the cryoablation procedure or by their local/personal physician. The enrolling physician will be responsible for providing the follow-up data to the registry and will, as appropriate, work with a subject's local/personal physician to collect the follow-up data.

A subject's Pre-surgery/Enrollment visit will include the collection of general demographics information, a brief medical history (general and renal specific), comorbidities, diagnosis details (imaging, biopsy) and current classes of medications. Subjects will be asked to complete a pre-surgery quality of life (SF-12) questionnaire. At the cryoablation visit, details of the cryotherapy procedure will be collected, as well as any potentially or directly related adverse events.

At the first post-cryoablation visit, data regarding initial outcomes and potentially or directly related complications, as applicable, will be collected, as will details regarding any post-operative interventional treatments. Data collection for subsequent follow-up visits will address delayed potentially or directly related complications, ongoing imaging and biopsy procedures as well as the introduction and continued use of new cancer treatments.

The schedule and number of follow-up visits for each subject will be determined by his/her physician's standard of care. Within this context, semi-annual to annual follow-up during the five-year follow-up period is generally anticipated though it is recognized that follow-up schedules will vary among enrolled subjects. The subject will be asked to complete the quality of life questionnaire post-cryoablation at the 6 and 12 month follow-up intervals if scheduled.

All potentially related and directly related cryoablation adverse events (AEs), serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) that occur within 30 days after

the cryoablation procedure is performed will be recorded. The cryoablation AEs, SAEs, and UADEs identified within the first 30 days after the cryoablation procedure will be followed and reported until resolution or for a period of 6 months.

Concomitant medications may be prescribed as per the physician's standard of care while the subject is participating in the registry. Only classes of concomitant medications will be collected at each follow-up visit.

6. Registry Population

6.1. Subject Enrollment

TRACE is anticipated to enroll approximately 250 subjects at approximately 10 sites who have undergone cryoablation of a renal lesion via a Galil Medical cryoablation system using Galil Medical needles. Subjects will be enrolled from a mix of academic and community-based physician sites.

To minimize selection bias within the enrolled subject population, participation in the registry is to be offered to all eligible patients on a consecutive basis as they present to the physician at each site. A log of eligible but non-enrolling patients will also be maintained. The log will include minimal health information regarding each non-enrolling patient (e.g., age, gender, reason for not enrolling) and will enable the evaluation of potential selection bias at periodic intervals throughout conduct of the registry. As the non-enrolled patients will not sign an informed consent form, their log data will be assigned an anonymous identifier and the data collected will not include personally identifiable information (as defined in 45 CFR 164.514).

6.2. Inclusion Criteria

Patients are required to meet all of the following criteria to be eligible for participation in the registry:

1. Patient is at least 18 years of age.
2. Patient has a renal lesion suspicious for malignancy.
3. Patient is to undergo renal lesion cryoablation via a Galil Medical cryoablation system using Galil Medical needles for treatment of primary or recurrent disease.
4. Patient is to be available for long-term follow-up per the enrolling physician's standard care practices.
5. Patient has provided written informed consent.

6.3. Exclusion Criteria

Patients who meet the following exclusion criteria are not eligible for enrollment in the registry:

1. Patient is either currently using or has used within the last 30 days an investigational product of any type.
2. Patient has metastatic disease to or from the kidney.

3. Patient has had previous therapy on the index lesion (e.g. radiofrequency, cryoablation, partial nephrectomy).

6.4. Renal Lesion Size

There are no strict exclusion criteria with regard to lesion size. The typical renal lesion suitable for cryoablation is ≤ 4 cm, however, as TRACE is an observational study of the real-world outcomes of cryoablation surgery using Galil Medical products, physicians are to use their training and experience to determine the size of a renal lesion that is appropriate for cryoablation.

6.5. Withdrawal of Subjects

Subjects may withdraw from the registry at any time, with or without reason and without prejudice to further treatment. As possible, the reason(s) for withdrawal (if given) will be recorded.

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7. Registry Assessments

The following table summarizes the data to be collected for each subject over the course of his/her TRACE participation.

Table 1: Registry Event Schedule

	Initial Collection of Data	Cryoablation Data	Subsequent Visit(s) Based Upon Site Standard of Care
Enrollment Date	X		
Informed Consent Obtained	X		
Demography	X		
Comorbidities	X		
Medical History	X		
Concomitant Medications	X		X
Imaging (Baseline)	X		
Quality of Life (SF-12)	X		X (6 & 12 mo)
Pre-Cryo Biopsy	X (if available)		
Pre-Cryo Pathology	X (if available)		
Intra-operative Biopsy		X (if available)	
Intra-operative Pathology		X (if available)	
Cryotherapy Procedure		X	
Intra-operative Complications		X	
Hospital Stay		X	X
Clinical Laboratories	X	X (if available)	X
Post-operative Complications		X	X
Post-operative Interventional Treatment		X	X
Follow-Up			X
Imaging Follow-up			X
Biopsy Follow-up			X (if available)
Pathology Follow-up			X (if available)
Primary Lesion Recurrence			X
New Renal Lesion Emergence			X
Emergence of new neoplastic disease (any type)			X
Development of metastatic disease			X
Withdrawal			X

7.1. Pre-Cryoablation Evaluation

Subjects will be enrolled in TRACE during their pre-cryoablation visit. The registry will collect data on the lesion characteristics, selected procedural parameters, associated safety measures, and short- and long-term clinical outcomes of the cryoablation procedure. The following information will be collected on all subjects entering the registry:

A. Data to be Collected by the Investigator and/or Study Coordinator

- Demographics (e.g., date of birth, gender, ethnicity)
- Height and weight
- ASA Classification
- Comorbidities (e.g., diabetes, hypertension, obesity, clotting disorder)
- Present Medical history
  - Incidental or symptomatic finding
  - Renal status
  - Previous renal surgery / History of suspicious lesion
- Cancer(s) other than renal
- Pertinent medication classes
- Smoking history
- Baseline Imaging
  - Type of imaging
  - Number of lesions identified (measures for each lesion should be recorded separately)
  - Lesion location: anterior, lateral, posterior, upper pole, mid-segment, lower pole, medial, hilar (within 5 mm of the renal hilum), with the following classification of the percentage of the mass that extends into the normal renal parenchymal border[6]
    - Exophytic- <40%
    - Mesophytic-40-60%
    - Endophytic- more than 60%
  - Lesion size measured by two methods:
    1) 3-dimensional measurements (cm) and
    2) Greatest trans-axial diameter (cm)
  - Lesion shape (spherical or non spherical)
  - Nephrometry Score
  - Hounsfield units
- Pre-Cryo Biopsy (if available)
  - Date
  - Type of biopsy (FNA or Core)
  - Number of cores taken
- Pre-Cryo Pathology (if available)
  - Classification of Lesion
  - Fuhrman Grade

- Clinical Laboratory Assessments (if available)
  - Creatinine
  - Estimated Glomerular Filtration Rate (eGFR)[5]
  - CBC (WBC, HCT, Hgb, Platelet)
  - BUN
  - LFT
  - PT
  - PTT

B. Baseline Quality of Life Questionnaire

Enrolled subjects will complete the Short Form-12 (SF-12) during the office visit. The SF-12 is a brief (twelve-item) health status survey to monitor outcomes in general and specific populations.

7.2. Cryoablation Procedure

The following data should be collected prior to or at the time of the procedure, as available.

- Procedure method (open, laparoscopic, percutaneous)
- Number of lesions treated with cryoablation
- Type of hemostatic agents or maneuvers used
- Lesion size measured by two methods:
  1) 3-dimensional measurements (cm) and
  2) Greatest trans-axial diameter (cm)
- Intra-operative biopsy (if available)
- Intra-operative pathology (if available)
- Hospital Stay
- Clinical laboratories (if available)
- Lesion location: anterior, lateral, posterior, upper pole, mid-segment, lower pole, medial, hilar (within 5 mm of the renal hilum), with the following classification of the percentage of the mass that extends into the normal renal parenchymal border[6]
  - Exophytic- <40%
  - Mesophytic- 40-60%
  - Endophytic- more than 60%
- Lesion shape (spherical or non spherical)
- Pathology of the lesion (if available)
- Number and type of cryosurgery needles used
- Number of freeze and thaw cycles
- Freeze and thaw times, per cycle
- Lowest temperature achieved at end of each freeze cycle
- Hilar clamping
- Embolization

- Galil needle cautery
- Method of thaw (active or passive)
- Method of monitoring iceball formation (US, CT, MRI)
- Involvement of the kidney's collecting system
- Post-operative HCT

7.3. Early Complications

The following data should be collected at the time of the procedure, or prior to discharge as applicable:

- Number and type of intra-operative complications
- Severity of complications
- Requirement for hospital admittance/stay
- Requirement for surgical intervention(s)

7.4. First Post-Operative Follow-Up

The following data should be collected at the first post-operative follow-up:

- Potentially related or directly related cryoablation adverse events
- Surgical intervention(s), as applicable

7.5. Ongoing Follow-Up Visits

It is anticipated that each subject will be seen at least once per year for a follow-up check-up. The following follow-up data, as available, will be collected for each subject:

- Potentially related or directly related delayed cryoablation adverse events
- Lab assessments (creatinine, estimated GFR)
- Imaging results
- Biopsy/pathology results if available
- Assessment of disease progression, including retreatment
- Emergence of a new renal lesion
- Emergence of new neoplastic disease (any type)
- Emergence of metastatic disease
- Quality of Life Assessment (SF-12) at 6 and 12 months post procedure

7.6. Withdrawal

Subjects will be encouraged to remain active in TRACE for the full five-year follow-up period, but they may withdraw from the registry at any time; the reason(s) for the withdrawal will be collected. All subjects who withdraw from the registry should be encouraged to participate in a follow-up/exit visit to collect final outcomes assessments and current cancer therapies. If an office visit is not possible, a telephone interview should be attempted.

8. Statistical Methods

8.1. Sample Size Estimate and Justification

Approximately 250 subjects are expected to participate in TRACE. As the registry is an observational, non-comparative study, power calculations have not been performed. The estimated sample size has been established to help ensure an adequate population of "completed subjects," defined as those subjects completing four or more years of follow-up, at the closure of the registry.

8.2. Missing Data

As TRACE is an observational registry of subjects and does not strictly define post-cryoablation subject follow-up, the frequency, volume and extent of data collected for each enrolled subject will vary. Missing data will not be imputed.

8.3. Analysis Populations

All subjects completing a cryoablation procedure for removal of a renal lesion will be included the analyses of TRACE data.

The full details of the approach to analysis of the data will be detailed in the Statistical Analysis Plan.

8.4. Measures

The parameters that will be analyzed include but may not be limited to the following:

<u>Baseline Assessments</u>

- Demographics
- Baseline characteristics
- Disease status
- Medical History

<u>Procedural Measures</u>

- Procedure method (open, laparoscopic, percutaneous)
- Number of lesions treated with cryoablation
- Type of hemostatic agents or maneuvers used
- Lesion size measured by two methods:
  1) 3-dimensional measurements (cm) and
  2) Greatest trans-axial diameter (cm)
- Intra-operative biopsy (if available)
- Intra-operative pathology (if available)
- Hospital Stay
- Clinical laboratories (if available)

- Lesion location: anterior, lateral, posterior, upper pole, mid-segment, lower pole, medial, hilar (within 5 mm of the renal hilum), with the following classification of the percentage of the mass that extends into the normal renal parenchymal border[6]
  - Exophytic- <40%
  - Mesophytic- 40-60%
  - Endophytic- more than 60%
- Lesion shape (spherical or non spherical)
- Pathology of the lesion (if available)
- Number and type of cryosurgery needles used
- Number of freeze and thaw cycles
- Freeze and thaw times, per cycle
- Lowest temperature achieved at end of each freeze cycle
- Hilar clamping
- Embolization
- Galil needle cautery
- Method of thaw (active or passive)
- Method of monitoring iceball formation (US, CT, MRI)
- Involvement of the kidney's collecting system
- Post-operative HCT

Safety Measures

- Evaluation of potentially or directly related cryosurgery adverse events

Outcome Measures

- Changes in lesion size reduction measured by two methods:
  1) 3-dimensional measurements (cm) and
  2) Greatest trans-axial diameter (cm)
- Renal function status as determined by the estimated Glomerular Filtration Rate
- Length of hospital stay
- Post-cryoablation lesion enhancement
- Post-cryoablation biopsy (if performed)
- Disease recurrence or progression as determined locally by an increase in lesion size, contrast enhancement, and/or biopsy
- Disease-specific survival rates
- Overall survival rates and times
- Quality of Life assessment
- Emergence of new neoplastic disease (any type)
- Development of metastatic disease

8.5. Analyses

Continuous variables (e.g., age) will be summarized by the number of subjects, mean, standard deviation, median, interquartile range, minimum and maximum. Categorical variables (e.g., race) will be summarized by frequencies and percentages of subjects in each category.
Reporting from the database may occur at 6 months and then on an annual basis or more frequently as determined.

Lesion size
Lesion size reduction will be determined by examining the change from baseline at follow-up visits. Method of post-treatment imaging including ultrasound, CT or MRI, use of contrast, enhancement and other imaging parameters will be reported for baseline and follow-up visits.

Renal function status
Renal function status will be determined by examining the estimated Glomerular Filtration Rate (eGFR) at baseline and follow-up visits. The estimated Glomerular Filtration Rate will be calculated using the Modification of Diet in Renal Disease (MDRD) formula.[5]
For creatinine in mg/dL:

$$eGFR = 175 \times Serum\ Creatinine^{-1.154} \times Age^{-0.203} \times [1.212\ \textit{if Black}] \times [0.742\ \textit{if Female}]$$

Disease recurrence or progression
Disease recurrence or progression will be determined locally by evidence of an increase in lesion size, contrast enhancement, and/or biopsy.

Disease-specific survival rate is defined as the time in days from cryoprocedure to death due to kidney cancer. Subjects who are alive will be censored at date of their last visit. Subjects who have died from causes other than kidney cancer will be censored at the time of death. Disease-specific survival rates will be summarized by using Kaplan-Meier methodology.

Overall survival rate is defined as the time in days from cryoprocedure to death. Subjects who are alive will be censored at the date of the last visit. Overall survival rates will be summarized by using Kaplan-Meier methodology.

Time to recurrence is defined as the time in days from cryoprocedure to disease recurrence or progression. Subjects without disease recurrence or progression will be censored at the date of their last visit or their date of death (due to any cause). Recurrence free survival rates will be summarized by using Kaplan-Meier methodology.

Intra-operative Data
Initial cryotherapy procedure information including the type of procedure, lesion size and number, cryosurgery needles used, freeze and thaw times, method of thaw (active or passive), method of monitoring iceball formation (US, CT, MRI), and temperatures reached will be summarized.

Intraoperative biopsy results including the classification of the lesion will be summarized.

Adverse, Serious, and Unanticipated Adverse Events

Cryosurgery-related intra-operative events, potentially related and directly related post operative cryoablation adverse events, serious adverse events and unanticipated adverse device effects will be summarized.

Involvement of the kidney's collecting system

Involvement of the kidney's collecting system will be assessed by reviewing physician responses directly related to the affect of the cryoablation procedure on the collecting system.

Quality of Life

Quality of life assessment will be made by examining the change in the SF-12 baseline scores to those reported post-operatively at 6 and 12 months.

9. Data Management

9.1. Data Collection

TRACE data will be collected using a web-based electronic data capture (EDC) system, Clinical Discovery Platform (CDP), Simplified Clinical Data Systems, LLC. (Milford, NH). The system will be fully validated and compliant with 21 CFR 11 guidance.

Participating sites will enter all subject data collected during the conduct of TRACE into the EDC system using the electronic case report forms (eCRFs) developed for each stage of the registry. The system will use dynamic eCRFs to ensure an efficient entry process and completion of all necessary forms based on the individual needs of each enrolled subject.

All sites will receive training on the proper use of the system and the data collection expectations for TRACE. Each site will be trained on how to create a new subject, enter data into the eCRFs, edit/update data on existing eCRFs, resolve queries and approve/sign-off on each form.

9.2. Data Processing

To help minimize data entry errors, the EDC system will include edit checks that will identify potential data issues at the time data submission. All eCRFs will be reviewed by clinical staff within Galil Medical to check for completeness and potential unresolved data entry issues. Galil Medical will generate queries within the system for open data issues and follow-up with each site as necessary to resolve key data element issues.

The investigator will review all eCRFs created and will approve each via electronic signature within CDP.

The TRACE database will be subject to periodic interim analyses based on key registry milestones. Prior to each milestone analysis, Galil Medical will work with each site to ensure a data set that is as complete and accurate as possible. At the conclusion of the registry, the database will undergo a final review and then be locked. No changes will be allowed in the database after the final lock without the written authorization of the appropriate TRACE management team members at Galil Medical.

10. Monitoring Procedures

10.1. Monitoring and Auditing

Participating TRACE sites will be managed remotely via regular telephone contact and, as necessary, on-site monitoring visits; no routine monitoring visits will be conducted. When necessary, site visits will be performed by an authorized representative from Galil and will be conducted according to applicable GCP and local regulatory guidelines.

In addition, sites may be subject to an audit visit by Galil or a local regulatory authority (e.g., FDA). If such a site audit occurs, the investigator agrees to provide access to all pertinent subject records, eCRFs and other site documents deemed necessary to complete the audit visit.

By signing the Registry Agreement, the investigator grants permission to authorized representatives of Galil and/or local regulatory authorities to conduct on-site monitoring visits for the purpose of reviewing the collected registry data and to review site procedures employed in the conduct of TRACE.

11. Adverse Events

All potentially related and directly related cryoablation adverse events (AEs), serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) that occur within **30 days after the cryoablation procedure** is performed will be recorded. The cryoablation AEs, SAEs, and UADEs identified within the first 30 days after the cryoablation procedure will be followed and reported until resolution or for a period of 6 months.

11.1. Definitions

Adverse Event (AE)

An AE is defined as any undesirable clinical occurrence in a subject potentially or directly related to the cryotherapy procedure. All AEs must be recorded in the electronic database. A description of the event, including the start date, resolution date, action taken and the outcome should be provided, along with the Physician's assessment of the relationship between the AE and the registry procedures.

The anticipated cryoablation related adverse events include the following: adjacent organ injury/Intra-operative injury, allergic reaction/hypersensitivity, angina, arrhythmia, atelectasis,

bleeding/hemorrhage, cardiac ischemia/myocardial infarction/heart attack, cardiac troponin T (cTnT), cardiopulmonary arrest (cause unknown, non-fatal), creatinine elevation, cystitis (requiring intervention), death NOS (not otherwise specified), delay/not healing, deep vein thrombosis (DVT), ecchymosis/bruising, edema/swelling, fever (in the absence of neutropenia), fistula (GI), glomerular filtration rate (GFR) elevation, hematoma, hematuria (requiring intervention), hypertension, hypotension, hypothermia, ileus, infection, injection site reaction, nausea, neuropathy, obstruction GI, obstruction GU, urinary retention, pain, pelvic vein thrombosis, perforation GU, perirenal fluid collection, pleural effusion (non-malignant), pneumothorax, probe site parathesia, prolonged chest tube drainage, prolonged intubation, pulmonary embolism, pulmonary failure, renal artery/renal vein injury, renal capsule fracture, renal failure, renal hemorrhage, renal infarct, renal obstruction NOS GU, renal vein thrombosis, seroma, skin burn/frostbite, stricture of the collection system or ureters/stricture/stenosis, stroke, thrombosis/thrombus/embolism, transient ischemic attach (TIA), UPJ obstruction, urinary fistula, urinary renal leakage, urinary retention/oliguria, vagal reaction, vomiting, wound complication, and wound infection.

This list of adverse events and their corresponding Common Terminology Criteria for Adverse Events (CTCAE) Terms are listed in Appendix B. The severity of adverse events will be graded by the physician using the categories from the CTCAE as listed in the database.

Serious Adverse Event (SAE)

Grade 4 or higher of the CTCAE guidelines and the following ICH definitions will be used in the protocol as applicable:

- Results in Death
- Is Life Threatening
  Note: the term 'life threatening' in the definition of serious refers to an event in which a subject was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolonged existing hospitalization
  Note: complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered to be an AE.
- Results in persistent or significant disability/incapacity
  Note: the term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma, that may interfere or prevent everyday life functions, but do not constitute a substantial disruption.
- Results in permanent impairment of a body structure or body function or requires surgical intervention to prevent permanent impairment of a body structure of body function

- Leads to fetal distress, fetal death or a congenital anomaly/birth defect
- Important medical events that may not be immediately life threatening, or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above should also usually be considered serious.
  Note: examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Unanticipated Adverse Device Event (UADE)

Any serious adverse effect on health or safety, or any life-threatening problem or death caused by or associated with an study device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application or any other unanticipated serious problem associated with an study device that relates to the rights, safety or welfare of the subjects.

11.2. Recording AEs, SAEs, and UADEs

Potentially and directly related cryoablation AEs (Appendix B) and SAEs/UADEs must be recorded on the eCRF. The investigator will review all documentation (e.g., hospital progress notes, laboratory, or diagnostic reports) relative to the event and record all relevant information regarding an AE/SAE/UADE in the eCRF.

The investigator will evaluate AEs using the following guidelines:

- Description of event (if the event consists of multiple signs and symptoms, a diagnosis should be recorded rather than each sign and symptom)
  - Record term and grade according to the CTCAE v.3.0 grading criteria
- Onset Date
- Stop Date
- Seriousness
  - The Physician must determine whether or not the AE meets the definition of serious as noted above and record in the eCRF. If the event is serious, the Physician must inform the Sponsor's designee within 24 hours of knowledge of the event and complete the SAE Report Form.
- Relationship to Study Procedure or Study Device
  - The Physician must make a causality assessment for all AEs and decide whether there is a reasonable possibility the AE was caused by the procedure or study device.
  - If there is a valid reason to suspect a causal relationship between the AE and the procedure or study device, the AE should be considered "directly related" or "potentially related" to the procedure or study device. Unless an AE can be excluded from causality, it must be

considered "potentially or directly related" to the procedure or study device.

- Clavien Classification
- Outcome
- Action Taken

11.3. Reporting Serious Adverse Events/Unanticipated Adverse Device Effects

Any potentially and/or directly related SAE or UADE must be reported by the investigator within 24 hours of learning of the event. The site must maintain adequate documentation of timely event reporting.

At any time the Galil Medical SAE reporting line can be reached at **651-287-5100**.

Additionally, an email may be sent to GalilSAE@galilmedical.com to report any potentially and/or directly related SAE or UADE.

A Galil Clinical Representative will work with the investigator to complete the SAE/UADE report. The investigator or designee must forward the requested follow-up information to the Galil Clinical Representative as the event continues and/or resolves. It is the responsibility of the investigator to inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of SAE/UADE as required by local procedure. Galil Medical is responsible for relaying adequate information on SAEs/UADEs to the all investigators as well as to regulatory authorities.

11.4. Grading of toxicity

Grading of toxicity will be done according to Common Terminology Criteria for Adverse Events (CTCAE, version 3.0). See anticipated adverse events in Appendix B.

12. Product Complaints

In the event of a Galil Medical cryoablation system or needle complaint, the investigator should contact the Galil Medical Customer Service Department at:

US:	877-639-2796
Europe:	44 1293459848
Israel:	972-4-9093200

13. Investigator Requirements

13.1. Registry Initiation

Prior to enrolling subjects in TRACE, investigator must provide the following documents to Galil or its designee:

- Signed and dated Registry Agreement

- Signed and dated Protocol Signature page
- Signed and dated Site Initiation Statement
- Signed and dated Financial Disclosure Certificate(s)
- A copy of the written IRB/IEC approval of the protocol (with membership roster)
- A copy of the written IRB/IEC approval of the Informed Consent Form
- A copy of the abbreviated curriculum vitae of the investigator
- A copy of the investigator's medical license

Participating site staff must also complete an initiation/training session with Galil Medical or another member at the site who is appropriately trained. The session will include a review of the protocol, discussion of the informed consent process, an overview of TRACE procedures and a practice session with the TRACE EDC system, when applicable.

13.2. Informed Consent

A sample Informed Consent Form (ICF) will be provided to each site. Any requested changes to the ICF must be reviewed and approved by Galil or its designee prior to submission to an IRB. If a modified ICF is used, a copy of the IRB-approved document along with the supporting IRB documentation must be submitted to Galil or its designee prior to its use within TRACE.

An approved ICF, including HIPAA language, must be signed by each subject, or the subject's legally authorized representative, before he/she is subject to any registry procedures. The investigator or designee must also sign and date the ICF to document the process. A copy of the ICF must be given to each subject, or the subject's legally authorized representative. The original signed ICF is to be kept with the subject's other TRACE records and must be made available for review upon request during any on-site monitoring or audit visits.

Prior to signing the ICF, the patient, or the patient's legally authorized representative, will be provided with an oral overview of the registry. This overview will include a discussion of the registry's purpose and objectives, the scope and duration of participation and the disclosure that he/she may withdraw from the registry at any time without consequence. All questions from the patient or his/her legally authorized representative are to be answered before the ICF is signed.

13.3. Institutional Review Board/Independent Ethics Committee

The TRACE protocol, the Informed Consent Form (ICF) and relevant supporting information must be submitted to an Institutional Review Board / Independent Ethics Committee (IRB/IEC) before a site is initiated for participation. Approval from the IRB/IEC must be obtained before any registry assessments are performed. IRB/IEC approval shall be documented in a letter to the physician, clearly identifying TRACE, the documents reviewed and the date of approval. TRACE will be conducted in accordance with applicable local regulatory and IRB/IEC requirements.

The investigator is responsible for keeping his/her local IRB/IEC apprised of the progress of the registry and of any protocol changes, as necessary. Galil Medical will be responsible for updating the registry's central IRB/IEC. The investigator is required to notify their local IRB/IEC of all adverse events that are both serious and unanticipated. Investigators under jurisdiction of the registry's central IRB/IEC are required to promptly notify Galil Medical of such events so that Galil Medical can notify the central review authority.

The investigator will be responsible for obtaining annual IRB/IEC approval and renewal throughout the duration of the registry.

13.4. Protocol Amendments

The TRACE protocol will only be altered by written amendments. Administrative changes that do not impact subject participation in the registry may be made without any further approvals. Any change that would require alteration of the Informed Consent form must receive approval from all persons who approved the original protocol and from the IRB/IEC prior to implementation. Following approval, the protocol amendment(s) will be distributed to all protocol recipients with instructions to append them to the protocol.

13.5. Record Retention

All source documents, records and reports related to data provided to the TRACE registry will be retained by the investigator in accordance with applicable ICH and CGP guidelines for at least two (2) years following closure of the registry. The investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. No records should be disposed of without the written approval of Galil.

14. Dissemination of TRACE Results

Galil is committed to disseminating the results of TRACE to the physician community regardless of the nature of those findings with respect to Galil's cryoablation products. Such data will be provided via abstracts, posters, presentations at scientific meetings and/or publication in peer-reviewed journals. Galil reserves the right to review all publications.

15. Registry Committees

15.1. Steering Committee

A Steering Committee of up to 7 to 10 members will be convened to oversee the conduct of TRACE. The committee will be comprised of recognized experts and thought leaders in cryoablation, as well as experts in epidemiology and biostatistics.

The committee will help guide the design of TRACE and will consult regarding the registry's implementation procedures. The committee will review the progress of the registry on an

ongoing basis and make recommendations regarding analyses of the collected data and dissemination of the registry's results, as well as guide the overall publication plan for TRACE.

16. Registry Administration

Galil or its designee will make necessary efforts to ensure that this registry is conducted in compliance with all applicable regulatory requirements.

16.1. Registry Discontinuation

Galil reserves the right to terminate the registry at any time. Reasons for terminating may include the following:

- Unsatisfactory enrollment
- Inability to ensure consistent follow-up data collection

16.2. Discontinuation of a Registry Site

Galil reserves the right to discontinue a site's participation in TRACE at any time. Possible reasons for discontinuation include:

- Site's discontinuation of use of Galil's cryoablation products
- Slower than agreed to registry enrollment
- Non-compliance with registry procedures
- Poor data quality
- Multiple or severe protocol violations without justification and prior approval
- Insufficient documentation and/or follow-up of SAEs

17. Bibliography

1. Goldfarb HA. Nd:YAG laser laparoscopic coagulation of symptomatic myomas. J Rep Med. 1993; 37: 636-638.
2. Saliken JC, Donnelly BJ, Rewcastle JC: The evolution and state of modern technology for prostate cryosurgery. Urology 2002; 60: 26–33.
3. Rewcastle JC, Sandison GA, Saliken JC, et al.: Considerations during clinical operation of two commercially available cryomachines. J Surg Oncol 1999; 71: 106–111.
4. Rewcastle JC, Hahn LJ, Saliken JC, et al.: Use of a moratorium to achieve consistent liquid nitrogen cryoprobe performance. J Surg Oncol 1997; 66: 10–113.
5. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann. Intern. Med. 1990; 130 (6): 461–70.
6. Finley DS, Beck S, Box G, et al.: Percutaneous and laparoscopic cryoablation of small renal masses. Urology 2008; 180: 492-498.

18. Appendices

18.1. Appendix A: Acronyms and Definitions

Acronym	Definition
AE	Adverse Event
ANC	Absolute Neutrophil Count
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDP	Clinical Discovery Platform
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FNA	Fine Needle Aspiration
GCP	Good Clinical Practices
HCT	Hematocrit
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB/IEC	Institutional Review Board/Independent Ethics Committee
LFT	Liver Function Test
MRI	Magnetic Resonance Imaging
PSM	Product Safety Manager
SAE	Serious Adverse Event
SF-12	Short Form 12
TRACE	Tracking Renal Tumors After Cryoablation Evaluation
UADE	Unanticipated Adverse Device Effects

18.2. Appendix B: Anticipated Adverse Event Terms

Adverse Events with the Common Terminology Criteria for Adverse Events v 3.0 (CTCAE) Short Name

Anticipated Adverse Event(s)	CTCAE Term
Adjacent organ injury/Intra-operative injury	Intraop injury – *Select*
Allergic reaction/hypersensitivity	Allergic reaction
Angina	Cardiac ischemia/infarction
Arrhythmia	Supraventricular Arrhythmia - *Select*
	Ventricular arrhythmia - *Select*
Atelectasis	Atelectasis
Bleeding/hemorrhage	Hemorrhage, GI – *Select*
	Hemorrhage, GU - *Select*
Cardiac ischemia/myocardial infarction/heart attack	Cardiac ischemia/infarction
Cardiac troponin T (cTnT)	cTnT
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest
Creatinine elevation	Creatinine
Cystitis (requiring intervention)	Cystitis
Death NOS (not otherwise specified)	Death not associated with CTCAE term – *Select*
Delay/not healing	Wound complication, non-infectious
DVT	Thrombosis/ thrombus/ embolism
Ecchymosis/bruising	Bruising
Edema/swelling	Edema: trunk/genital
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 109/L)	Fever
Fistula, GI	Fistula, GI – *Select*
Glomerular filtration rate (GFR) elevation	GFR
Hematoma	Hematoma
Hematuria (requiring intervention)	Hemorrhage, GU – *Select*
Hypertension	Hypertension
Hypotension	Hypotension
Hypothermia	Hypothermia
Ileus	Ileus

Infection (documented clinically) with Grade 3 or 4 ANC	Infection (documented clinically) with Grade 3 or 4 ANC – *Select*
Infection with normal ANC	Infection with normal ANC – *Select*
Infection with unknown ANC	Infection with unknown ANC – *Select*
Infection	Infection – Other (Specify)
Injection site reaction/ extravasation changes	Injection site reaction
Nausea	Nausea
Neuropathy: Motor	Neuropathy-motor
Neuropathy: Sensory (e.g., lumbar radiculopathy)	Neuropathy-sensory
Obstruction, GI (e.g., colon, rectum)	Obstruction, GI – *Select*
Obstruction, GU (bladder, ureter, urethra)	Obstruction, GU – *Select*
Pain	Pain – *Select*
Pelvic vein thrombosis	Thrombosis/thrombus
Perforation, GU	Perforation, GU – *Select*
Perirenal fluid collection	Leak, GU – *Select*
Pleural effusion (non-malignant)	Pleural effusion
Pneumothorax	Pneumothorax
Probe site parathesia (tingling, numbness)	Neuropathy-sensory
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation
Pulmonary embolism	Thrombosis/ thrombus/ embolism
Pulmonary failure/ARDS	ARDS
Pulmonary failure/hypoxia	Hypoxia
Renal artery/renal vein injury	Vascular – Other (Specify)
Renal capsule fracture	Intraop injury – *Select*
Renal failure	Renal failure
Renal hemorrhage	Hemorrhage, GU – *Select*
Renal infarct	Renal, other (Specify)
Renal obstruction NOS, GU	Renal, other (Specify)
Renal vein thrombosis	Thrombosis/ thrombus/ embolism
Seroma	Seroma
Skin burn/frostbite	Burn
Stricture of the collection system or ureters/stricture/stenosis	Stricture, anastomotic, GU

Stroke	CNS ischemia
Thrombosis/embolism (vascular access)	Thrombosis/embolism (vascular access)
Thrombosis/thrombus/embolism	Thrombosis/ thrombus/ embolism
TIA (transient ischemic attack)	CNS ischemia
UPJ obstruction	Obstruction, GU-*Select*
Urinary fistula	Fistula, GU – *Select*
Urinary renal leakage	Leak GU – *Select*:
Urinary retention/oliguria	Urinary retention
Vagal reaction	Vasovagal episode
Vomiting	Vomiting
Wound complication (hernia, dehiscence)	Wound complication, non-infectious
Wound infection (abscess, skin infection)	Infection, other