Protocol No. CUC10-RNL02-03 (20May2011)

Tracking Renal Tumors After Cryoablation Evaluation (TRACE)

Statistical Analysis Plan

Prepared by Galil Medical

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Revision History

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Final Version 2.0	19Mar2018	Nikhil Chauhan	Updated to new SAP format and added further details
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SIGNATURE PAGE

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

AE	Adverse event
AKP	Alkaline phosphatase (plasma)
ALP	Alkaline phosphatase (serum)
ALT	Alanine aminotransferase
AP	Anteroposterior
ASA	American Society of Anesthesiologists
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Bodily pain
BUN	Blood urea nitrogen
CC	Craniocaudal
CI	Confidence interval
CKD	Chronic kidney disease
CT	Computed tomography
CTCAE	Common toxicity criteria for adverse events
DSS	Disease-specific survival
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ENT	Ear nose and throat
FDA	Food and Drug Administration
HCT	Hematocrit
HIV	Human immunodeficiency virus
INR	International normalized ratio
IR	Interventional radiologist
ITT	intent-to-treat
NOTES	Natural orifice transluminal endoscopic surgery
Max	Maximum
MCS	Mental component summary
MDRD	Modification of diet in renal disease
MH	Mental health
Min	Minimum
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NS	Nephrometry score
OS	Overall survival
QoL	Quality of life
p25	25^{th} percentile
p75	75^{th} percentile

PCS	Physical component summary
PF	Physical functioning
PT	Prothrombin time
PTT	Partial thromboplastin time
RCC	Renal cell carcinoma
RE	Role emotional
RP	Role physical
SAE	serious adverse event
SAP	Statistical analysis plan
sCR	Serum creatinine
SD	Standard deviation
SF	Social functioning
TBIL	Total bilirubin
TR	Transverse
TTR	Time to recurrence
UADE	Unanticipated adverse device effect
USA	United States of America
VT	Vitality
WBC	White blood cell

2 INTRODUCTION

Galil Medical's commercially available cryotherapy systems and associated needles are United States of America (USA) Food and Drug Administration (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 in the specialty fields described above by the direct application of temperatures as low as −80°C to −90°C. Cryoablation procedures using Galil's systems may be performed as open, laparoscopic, or percutaneous procedures under imaging guidance: ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI). 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 STUDY OBJECTIVES

The primary objective of the study is to assess the short- and long-term outcomes of patients who undergo renal lesion ablation via cryotherapy with products offered by Galil Medical.

Secondary objectives are:

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

4 STUDY DESIGN

4.1 General Design

This is an observational, open-label, single-arm, multi-center study of patients who have undergone renal lesion cryoablation per their physician's standard of care via a Galil Medical cryoablation system using Galil Medical needles.

Data for patients who agree to participate are collected prospectively. (i.e., registry data collection).

TRACE is anticipated to enroll approximately 250 patients at approximately 10 sites.

Patients will be enrolled from a mix of academic and community-based sites.

The schedule and number of follow-up visits for each patient 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 anticipated though it is recognized that follow-up schedules will vary among enrolled patients. Planned per-patient follow-up is 5 years.

The results 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 provide information on long-term surveillance of patients undergoing renal lesion cryoablation.

In addition, this 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 for treatment and follow-up assessments.

4.2 Method of Assignment of Patients to Treatment Groups

Eligible patients at participating sites will be enrolled in this single arm study.

To minimize patient selection bias, 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.

4.3 Blinding

This is a single arm, open label study, and there is no blinding.

4.4 Determination of Sample Size

Approximately 250 patients 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 patients," defined as those patients completing four or more years of follow-up, at the closure of the registry. This study is not powered for formal statistical analysis.

5 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

5.1 Changes in the Conduct of the Study

Patients were enrolled in the following three versions of the study protocol:

- CUC10-RNL02-01 (15Feb2010)
- CUC10-RNL02-02 (28Apr2011)
- CUC10-RNL02-03 (20May2011).

There were no changes that are likely to have an impact on the statistical analysis of the study data.

5.2 Changes in the Planned Analyses

The following are changes from the planned analyses in the current version of the study protocol or in the previous version of the statistical analysis plan (SAP):

- The protocol and previous SAP, listed 'Emergence of new neoplastic disease (any type)' as a study outcome. However, data to assess this outcome was not recorded in the electronic case report form (eCRF) so this outcome cannot be assessed.
- 'Track ablation' was listed in the previous SAP as a procedural/intra-operative endpoint, and this same endpoint was described as 'Galil needle cautery' in the study protocol. However, this data (i.e., needle track ablation/Galil needle cautery) was not recorded in the eCRF so this variable cannot be assessed.
- Method of thaw was listed as having the following 3 options in the SAP: active, FastThaw, and passive. However, FastThaw, which is a type of active thaw, is not included as an option in the current protocol or the eCRF.
- Steering Committee review of draft tables, figures and listings (dated 08May2018) resulted in the following changes
    - In the analysis of time to recurrence, progression will not be considered to be an event of interest
    - AE tables and summaries of renal function will be prepared for both ITT and RCC populations; previously these tables were only prepared for the ITT population
    - Updated tables of post-cryoablation lesion enhancement
    - New table of post-cryoablation lesion enhancement by subgroups of baseline lesion classification (i.e., exophytic, mesophytic, endophytic)

6 BASELINE, EFFICACY AND SAFETY EVALUATIONS

6.1 Schedule of Evaluations

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

Table 2 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

6.2 Time Point Algorithms

6.2.1 Relative Days

Relative days will be calculated for both efficacy and safety endpoints. The date of cryoprocedure will be considered relative day 1, and the day before the cryoprocedure will be relative day -1. Patients could also have received subsequent cryoprocedures, and these are recorded in the eCRF page named "Follow-up/Further Cancer Therapy" and not on an additional eCRF page named "Cryotherapy Procedure." For the purposes of this SAP, date of cryoprocedure refers to the date of the first cryoprocedure. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days):

For days on or after cryoprocedure:
Date of assessment – Date of cryoprocedure + 1

For days before cryoprocedure:
Date of assessment – Date of cryoprocedure

6.2.1.1 Partial Dates

Partial dates are not permitted in the database.

6.2.2 Windows

For the purpose of statistical analysis, visit windows will be calculated as shown below.

Table 2 Analysis Windows for follow-up assessments

Analysis visit name	Visit window (months)	Visit window for analysis (days)
Pre 6 Month	0 to 3	1 to 92
6 Month	3 to 9	93 to 275
12 Month	9 to 18	276 to 549
24 Month	18 to 30	550 to 915
36 Month	30 to 42	916 to 1281
48 Month	42 to 54	1282 to 1647
60 Month	54 to 66	1648 to 2013
Post 60 Month	>66	>2013

Day 1 = date of cryoprocedure

If a patient has more than one assessment occurring in the same visit window, a manual review on a patient-by-patient basis will be performed by Galil Medical to select the analysis visit and will be documented. The assessment to be used will be selected based on completeness of the data and whether or not recurrence is known versus suspected. For example, if imaging at month 13 suggests recurrence and further imaging at month 15 confirms there is/is not recurrence, the confirmatory imaging assessment will be used. If

data between multiple assessments is considered to be similar, the assessment closest to the middle of the visit window will be used.

6.3 Baseline Assessments

Baseline is defined as any assessment performed on or before the day of cryoprocedure.

The following baseline assessments will be recorded prior to cryoprocedure:

- Informed Consent
- Inclusion/ Exclusion Criteria
- Demographics (age, gender, race, ethnicity)
- Height, weight, body mass index (BMI)
- American Society of Anesthesiologists (ASA) physical status classification
- Medical history
- Prior medications and therapies
- Smoking history
- Disease and treatment history
- Laboratory tests (hematology, coagulation, chemistry)
- SF-12 quality of life (QoL)
- Lesion assessments by imaging
- Biopsy and pathology (if available)
- Nephrometry score (NS)

Hounsfield units are recorded in the eCRF for each lesion included in the imaging assessments, separately for the following phases:

- Non-contrast
- Arterial Phase
- Venous Phase
- Delayed Phase.

An increase of ≥15 units from the non-contrast phase to any of the 3 other phases will be considered, for the purposes of this SAP, to be an area suspicious for lesion recurrence according to Hounsfield units.

The NS uses the R.E.N.A.L. scoring system. It is based on the 5 most reproducible features that characterize the anatomy of a solid renal mass:

- (R)adius (scores tumor size as maximal diameter)
- (E)xophytic/endophytic properties of the lesion
- (N)earness of the deepest portion of the lesion to the collecting system or renal sinus
- (A)nterior (a)/posterior (p)
- (L)ocation relative to the polar line.

All components except for (A) are scores of 1, 2, or 3. The (A) describes the principal mass location to the coronal plane of the kidney. The suffix 'x' is assigned to the lesion if an anterior or posterior designation is not possible. An additional suffix 'h' is used to designate a hilar location of the lesion (abutting the main renal artery or vein). The total NS is computed as the sum of the R, E, N and L components, and a total NS of 4 to 6 is considered low complexity, 7 to 9 is considered moderate complexity, and 10 to 12 is considered high complexity. The range of complexity of a renal lesion's NS is from the simplest 4a (1+1+1+a+1) to the most complex 12ph (3+3+3+ph+3) (Kutikiv and Uzzo, 2009).

6.4 Efficacy Variables

For all efficacy evaluations, the baseline measurement is defined as the most accurate measurement prior to cryoprocedure; it may or may not be taken on the day of the procedure.

The efficacy endpoints for this study are:

- Changes in lesion size and volume measured as follows:
  - Volume computed from 3-dimensional measurements (cm) and
  - Greatest trans-axial diameter (cm)
- Post-cryoablation lesion enhancement
- Post-cryoablation biopsy (if performed)
- Disease recurrence or progression as determined locally by physician interpretation based on increase in lesion size, contrast enhancement, and/or biopsy
- Disease-specific survival rates
- Overall survival rates and times
- QoL assessment
- Development of metastatic disease

6.4.1 Changes in lesion size and volume

All lesion measurements referred to in this SAP will be the investigator interpreted imaging results (i.e., not the non-investigator interpreted results recorded in the eCRF), unless otherwise stated.

Change from baseline in lesion size and percentage change from baseline will be computed separately for each lesion.

For the 3-dimensional measurement the change from baseline in each of the three size measurements (i.e., anteroposterior [AP] (sagittal plane), transverse [TR] (axial plane), and craniocaudal [CC] (coronal/frontal plane) will be computed. The volume of each lesion will be computed as

$$\text{Lesion volume } (cm^3) = \frac{4}{3}\pi \text{ x AP/2 x TR/2 x CC/2,}$$

and the change from baseline in the volume measurement will then be computed for each lesion.

In addition to the per-lesion computation above, for patients with multiple lesions, the change from baseline in lesion volume will be computed for the lesion with maximum greatest trans-axial diameter, so that a per-patient analysis can also be performed with one value per patient.

Hounsfield units are recorded in the eCRF for each lesion included in the post-treatment imaging assessments, separately for the following phases:

- Non-contrast
- Arterial Phase
- Venous Phase
- Delayed Phase.

An increase of ≥15 units from the non-contrast phase to any of the 3 other phases will be considered, for the purposes of this SAP, to be an area suspicious for lesion recurrence according to Hounsfield units.

6.4.2 Post-cryoablation lesion recurrence with enhancement and lesion progression with enhancement

A lesion is considered to have post-cryoablation recurrence with enhancement if the response to the question "What is the status of the lesion?" in the follow-up lesion assessment eCRF page, is "Recurrent" and the response to the question "If Progressing or recurrent, was the lesion identified by contrast enhancement?" is "Yes" in the follow-up lesion assessment eCRF page. This endpoint will be recorded separately for each lesion.

A lesion is considered to have post-cryoablation progression with enhancement if the response to the question "What is the status of the lesion?" in the follow-up lesion assessment eCRF page, is "Progressing" and the response to the question "If Progressing or recurrent, was the lesion identified by contrast enhancement?" is "Yes" in the follow-up lesion assessment eCRF page. This endpoint will be recorded separately for each lesion.

In order to perform a per-patient analysis, for patients with multiple lesions, the lesion with maximum greatest trans-axial diameter will be considered.

6.4.3 Post-cryoablation biopsy

The endpoint of interest to assess post-cryoablation biopsy is the "Yes" or "No" response to the question "Was a biopsy performed on this lesion?" in the follow-up lesion assessment eCRF page. This endpoint will be recorded separately for each lesion.

In order to perform a per-patient analysis, for patients with multiple lesions, the lesion with maximum greatest trans-axial diameter will be considered.

6.4.4 Disease recurrence

Time to recurrence (TTR) is defined as the time from date of cryoprocedure to disease recurrence with enhancement in at least one lesion. A lesion is considered to have disease recurrence if the response to the question "What is the status of the lesion?" in the follow-up lesion assessment eCRF page, is "Recurrent", and there is a "Yes" response to the related question, "If Progressing or recurrent, was the lesion identified by contrast enhancement?"

6.4.5 Disease-specific survival

Disease-specific survival (DSS) is defined as the time from date of cryoprocedure until date of death due to kidney cancer. Deaths due to kidney cancer will be identified by a manual review, performed by Galil Medical, of the causes of death recorded in the study database.

6.4.6 Overall survival

Overall survival (OS) is defined as the time from date of cryoprocedure until date of death due to any cause.

6.4.7 Quality of Life

The following ten SF-12 scores, which are computed within the eCRF, will be separately analyzed, as change from baseline and by percentage change from baseline:

- General Health (GH)
- Physical Functioning (PF)
- Role Physical (RP)
- Bodily Pain (BP)
- Vitality (VT)
- Social Functioning (SF)
- Mental Health (MH)
- Role Emotional (RE)
- Mental Component Summary (MCS)
- Physical Component Summary (PCS).

6.4.8 Development of metastatic disease

The endpoint of interest to assess the development of metastatic disease is the "Yes" or "No" response to the question "Is there evidence of metastatic disease?" in the follow-up eCRF page. Per the Steering Committee, metastatic disease is limited to metastases to or from the kidney.

6.4.9 Additional efficacy assessments

Lesion status (i.e., responses to the question "What is the status of the lesion?" in the follow-up lesion assessment eCRF page), will be assessed.

6.5 Safety Assessments

6.5.1 Procedural and intra-operative data

The following will be included in the presentation of procedural and intra-operative data:

- Procedure method (i.e., the response to the question "What was the surgical approach?" in the eCRF)
- Surgical approach type
- Type of Galil Medical cryoablation system used (i.e., the response to the field "Type of cryotherapy system used on patient" in the eCRF)
- Method of monitoring used to place cryoablation needles
- Method of monitoring iceball formation
- Completion of cryotherapy
- Who performed the procedure?
- Type of anesthesia used
- Total anesthesia time
- Estimated blood loss during procedure
- Total duration of operation
- Type of hemostatic agents or maneuvers used
- Number of lesions identified at baseline but not treated with cryoablation
- Number of lesions treated with cryoablation
- Number and type of cryosurgery needles used
- Number of freeze and thaw cycles
- Total freeze time over all cycles; i.e., the sum of the times recorded in the eCRF fields: "Duration of active freeze"
- Total thaw time over all cycles; i.e., the sum of the times recorded in the eCRF fields: "Duration of thaw"
- Lowest temperature achieved at end of all freeze cycles, separately for temperature at the center and at the periphery
- Lesion in right or left kidney?
- Hilar clamping performed?
- Method of thaw
- Was embolization performed prior to cryoblation?
- Involvement of the kidney's collecting system, according to the following fields on the eCRF:
    - Did the iceball appear to touch the collection system?

  - Did the iceball appear to involve (engulf) the collection system?
  - Was there evidence for new gross hematuria during the course of the procedure potentially due to involvement of the iceball with the collecting system?
- Post-operative hematocrit (HCT)
- Were other surgical procedures performed during the patient's hospital stay?
- Was an extended hospital stay needed due to an adjunct procedure?
- Achievement of technical success at first post-cryoablation imaging assessment

Time from initial diagnosis of the suspicious renal mass to the date of cryoprocedure will be calculated as follows:
Time from diagnosis of suspicious renal mass (in months) =
(Date of cryoprocedure – Date of diagnosis + 1)/30.4375.

Length of hospital stay (in hours) will be computed using the discharge date and time and the admission date and time recorded on the eCRF.

A patient will be considered to have achieved technical success at first post-cryoablation imaging assessment according to the table below. NB: if any one of the three eCRF fields in the table below have missing data then technical success will also be set to missing.

eCRF field: Was cryotherapy completed?	**eCRF field: What is the status of this lesion? (at first post-cryoablation imaging assessment)**	**eCRF field: If progressing or recurrent, was the lesion identified by contrast enhancement? (at first post-cryoablation imaging assessment)**	**Derivation of technical success (at first post-cryoablation imaging assessment)**
"Yes"	"No longer present", "Smaller", or "Stable or no change"	This field should not be completed	"Yes"
"Yes"	"Progressing", or "Recurrent"	"No"	"Yes"
"Yes" or "No"	"Progressing", or "Recurrent"	"Yes"	"No"

6.5.2 Adverse Events

Intra-operative device complications will be recorded, and whether or not the complication was related to the malfunction of the cryoablation system. Intra-operative patient complications will also be recorded.

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 will be recorded.

The investigators will use the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events [CTCAE] (version 3.0) grading system, and also the Clavien classification. AE terms will be selected from a pre-specified code list within the eCRF, and will be auto-coded within the eCRF using the CTCAE Short Term.

The incidence of AEs will be the number of patients who had the AE (counted only once) divided by the number of patients in the analysis population and represented as a percentage.

6.6 Other Variables

6.6.3 Renal function

6.6.3.1 Estimated Glomerular Filtration Rate

The estimated Glomerular Filtration Rate (eGFR) will be calculated within the eCRF using the Modification of Diet in Renal Disease (MDRD) formula. For serum creatinine (sCR) in mg/dL, and age in years:

eGFR =175 x sCR -1.154 x Age-0.203 x [1.212 if Black] x [0.742 if Female].

The change from baseline in eGFR will be computed.

6.6.3.2 Chronic Kidney Disease stages

Chronic kidney disease (CKD) stages will be computed from the eGFR values as follows:

- Stage 1: eGFR ≥90 mL/min
- Stage 2: eGFR ≥60 and <90 mL/min
- Stage 3A: eGFR ≥45 and <60 mL/min
- Stage 3B: eGFR ≥30 and <45 mL/min
- Stage 4: eGFR ≥15 and <30 mL/min
- Stage 5: eGFR <15 mL/min

The change from baseline in CKD stages will be computed.

6.6.3.3 Serum creatinine (sCR)

The change from baseline in sCR will be computed.

7 STATISTICAL METHODS

7.1 General Methodology

All statistical tests will be two-sided with a significance level of α=0.05, unless specified otherwise, and will be performed using SAS® Version 9.4 or later. Data will be summarized

using descriptive statistics (number of patients [n], mean, standard deviation [sd], median, interquartile range, minimum, and maximum) for continuous variables and using frequency and percentage for discrete variables.

Patient listings of all data from the case report forms (eCRF) as well as any derived variables will be presented.

7.2 Adjustments for Covariates

The following covariates will be included, one at a time, in 'univariable' Cox regression analysis of time-to-event efficacy endpoints.

- Age (continuous as age*10 to assess 10 year risk)
- Gender
- Race
- Maximum lesion size (≤4cm, >4 cm) at baseline using the greatest trans-axial diameter
- Number of cryosugery needles used
- Type of needles used
    - Needles with the cautery feature (IceRod CX, IceFORCE 2.1 CX, IcePearl 2.1 CX) vs other types; a patient is deemed to be in the 'Needles with the cautery feature' group if any needle used in that patient was of that type
- Duration (in months) from date of initial diagnosis of the suspicious renal mass to cryoprocedure (continuous variable)
- Baseline eGFR (continuous variable)
- Histological type (conventional renal cell carcinoma [RCC] versus other)
- BMI (continuous variable)
- ASA classification
- NS complexity category at baseline (low, moderate, high) (as defined in Section 6.3)
- Cryoprocedure surgical approach
    - Note: there is only one patient with an open procedure, so only laparoscopic and percutaneous procedures will be included in this analysis
- Prior renal surgery
- Prior abdominal surgery
- Solitary kidney (yes versus no); a patient is considered to have a 'yes' for this variable if 'Nephrectomy' is selected on the Medical History eCRF page.
- History of hypertension
- History of diabetes
- Use of anticoagulants

All factors in the univariable models with a two-sided p-value <0.15 will be included in a multivariable analysis to determine the impact of these factors.

The following covariates will be included, one at a time, in 'univariable' logistic regression analysis of the occurrence of an adverse event (AE).

- Age (continuous as age*10 to assess 10 year risk)
- Gender
- Race
- Maximum lesion size (≤4cm, >4 cm) at baseline using the greatest trans-axial diameter
- Number of cryosugery needles used
- Type of needles used
    - Needles with the cautery feature (IceRod CX, IceFORCE 2.1 CX, IcePearl 2.1 CX) vs other types; a patient is deemed to be in the 'Needles with the cautery feature' group if any needle used in that patient was of that type
- Histological type (conventional renal cell carcinoma [RCC] versus other)
- BMI (continuous variable)
- ASA classification
- NS complexity category at baseline (low, moderate, high) (as defined in Section 6.3)
- Cryoprocedure surgical approach
    - Note: there is only one patient with an open procedure, so only laparoscopic and percutaneous procedures will be included in this analysis
- Prior renal surgery
- Prior abdominal surgery
- Solitary kidney (yes versus no); a patient is considered to have a 'yes' for this variable if 'Nephrectomy' is selected on the Medical History eCRF page.
- Baseline lesion classification (i.e., exophytic, mesophytic, endophytic).
- History of hypertension
- History of diabetes
- Use of anticoagulants

All factors in the univariable model with a two-sided p-value <0.15 will be included in a multivariable analysis to determine the impact of these factors.

7.3 Handling of Dropouts or Missing Data

Dropout patients will not be replaced in this study. The handling of missing data will be discussed throughout Section 8, where relevant. Censoring for the efficacy endpoints is discussed in Sections 6.4.1 and throughout Section 8, where applicable.

7.4 Interim Analyses

Interim analyses will performed as requested by the Steering Committee.

7.5 Multiple Comparisons/Multiplicity

Since this is a single arm registry study, no adjustment for multiple testing will be performed.

7.6 Examination of Subgroups

Subgroup analyses required for individual endpoints are described in Section 8.

8 STATISTICAL ANALYSIS

8.1 Disposition of Patients

The number of patients enrolled will be summarized by analysis population (see Section 8.3) and by site. The number of patients who completed the study, the number of patients ongoing in the study (for interim analyses), and the number of patients who discontinued from the study and the reasons for discontinuing (e.g., withdrew consent, lost to follow-up, death, other) will also be summarized.

Duration of follow-up is defined as the time from cryoprocedure until date of death due to any cause or date when patient was known to be alive.

Duration of follow-up (months) =

(Date of death/last known alive – Date of cryoprocedure + 1) / 30.4375

Duration of follow-up will be summarized using descriptive statistics. The number and percentage of patients with follow-up up to the following timepoints will also be provided:

- 1 month
- 3 months
- 6 months
- 12 months
- 24 months
- 36 months
- 48 months
- 60 months.

The number of patients who have completed each follow-up visit will be provided based on the analysis windows derived from the lesion assessment follow-up dates. The corresponding percentage of patients will be based on the number of patients who remain in follow-up at that visit (i.e. excluding patients who have withdrawn, died or completed after the end date of the analysis window). For example, if a patient withdrew from the study or died within the 36 month analysis visit window, the patient would be included in

the 36 month visit percentage calculation, but would not be included in the percentage calculations for subsequent visits.

The number of patients censored for the time-to-event endpoints, together with a breakdown of the reasons for censoring, will also be summarized.

8.2 Protocol Deviations

Since this is a registry study, protocol deviations/violations will not be recorded.

8.3 Analysis Populations

8.3.1 Intent To Treat (ITT) Population

All patients where a cryoprocedure was attempted with a Galil Medical Cryoablation System and needles and who met the study eligibility criteria will form the Intent-to-Treat (ITT) population. This population will be used for the analysis of all efficacy and safety data. Patients in the ITT population will be identified as follows:

1) First include all patients with a date of cryotherapy recorded
2) Then exclude any patients who have been manually identified as having not met all eligibility criteria from a review of monitoring reports.

8.3.2 Renal Cell Carcinoma (RCC) Population

The RCC population will be comprised of patients in the ITT population, with biopsy proven RCC and at least one lesion treated. Patients with biopsy proven RCC will be identified as patients having any of the following responses to either of the two questions "What is the frozen section pathology result?" and "What is the permanent section pathology result?

- Conventional, Renal Cell Carcinoma
- Papillary Renal Cell Carcinoma
- Chromophobe Renal Cell Carcinoma
- Collecting Duct Renal Cell Carcinoma
- Renal Cell Carcinoma, unclassified

Patients with a single lesion treated will be identified using the eCRF field "Number of lesions subjected to cryoablation" on the Procedure eCRF page.

This population will be used for the analysis of efficacy and AE data.

8.4 Demographic and Other Baseline Characteristics

All demographic and baseline summaries will be displayed for the ITT and RCC populations.

Gender, race, ethnicity, will be summarized using counts and percentages. Age (at date of cryoprocedure, computed using the date of birth), height, weight and BMI will be summarized with descriptive statistics (number of patients [n], mean, standard deviation (SD), median, 25th percentile (p25), 75th percentile (p75) minimum (min), and maximum (max)). Age group (≥18 to <65 years, ≥65 to <75 years, and ≥75 years) will be summarized using counts and percentages.

The ASA physical status classification will be summarized using counts and percentages. The number and percentage of patients with medical history events will be summarized. Also, the number and percentage of patients with a history of smoking (current smoker, ex-smoker, never been a smoker) will be given.

Disease related baseline characteristics will be summarized using counts and percentages as follows:

- Previous renal surgery
- On dialysis
- Kidney affected
- Index lesion an incidental or symptomatic finding
- Recurrent disease
- Total number of lesions subjected to cryoablation
- Biopsy performed on the lesion to be treated during the cryoprocedure for the study (note: if multiple lesions were treated, each lesion may not have individual biopsy results)
- At least one malignant lesion by frozen section pathology; a response of "Malignant" in the eCRF field of "What is the frozen section pathology result?" will be classed as a "Yes" for this endpoint, and responses of "Benign", "Not otherwise specified", or "Not Done" will be classed as a "No".
- At least one malignant lesion by permanent section pathology; a response of "Malignant" in the eCRF field of "What is the permanent section pathology result?" will be classed as a "Yes" for this endpoint, and responses of "Benign", "Not otherwise specified", or "Not Done" will be classed as a "No".

Maximum lesion size, using the greatest trans-axial diameter, will be summarized with descriptive statistics and also as categories of ≤4 cm and >4 cm. The maximum lesion volume will also be summarized.

The following lab parameters will be summarized with descriptive statistics:

- eGFR
- sCR; will also be summarized separately for patients with a history of hypertension, for patients with a history of diabetes, for patients with a

history of both hypertension and diabetes; and by NS categories at baseline of low, moderate and high complexity (as defined in Section 6.3).
  - Blood urea nitrogen (BUN)
  - White blood cell (WBC)
  - Hematocrit
  - Hemoglobin
  - Platelets
  - Alanine aminotransferase (ALT)
  - Aspartate aminotransferase (AST)
  - Alkaline phosphatase (serum) (ALP)
  - Alkaline phosphatase (plasma) (AKP)
  - Total bilirubin (TBIL)
  - International normalized ratio (INR)
  - Prothrombin time (PT)
  - Partial thromboplastin time (PTT)

CKD stages at baseline will be summarized with counts and percentages.

The total NS at baseline will be summarized with descriptive statistics, and also according to the categories of low, moderate and high complexity (as defined in Section 6.3). The individual R, E, N, A and L components of the NS will be summarized with counts and percentages. NS at baseline will also be summarized separately for patients with a history of hypertension, for patients with a history of diabetes, and for patients with a history of both hypertension and diabetes.

The following lesion characteristics will be summarized in a per-lesion summary (i.e., over the total number of lesions recorded in the study for descriptive statistics, and as a percentage of the total number of lesions for categorical data):

- Lesion size, by greatest trans-axial diameter, will be summarized with descriptive statistics and also as categories of ≤4cm and >4 cm
- Lesion volume will be summarized with descriptive statistics
- Duration (months) between date of baseline imaging and date of cryoprocedure will be summarized with descriptive statistics
- The type of imaging used (CT, MRI, ultrasound)
- Lesion location
- Lesion classification
- Lesion shape
- Cystic or solid lesion
- Hounsfield units, separately for each of following phases
  - Non-contrast
  - Arterial Phase
  - Venous Phase
  - Delayed Phase

- Area suspicious for lesion recurrence according to Hounsfield units (as defined in Section 6.3)
- The following biopsy related data will be summarized for all patients and separately by each site
  - Biopsy performed?
  - Duration (months) between date of biopsy sample and date of cryoprocedure will be summarized with descriptive statistics
  - Type of biopsy
  - If a core biopsy was performed, number of cores taken
  - Frozen section pathology result
  - Frozen section pathology classification
  - Permanent section pathology result
  - Permanent section pathology classification
  - Fuhrman classification grade

8.5 Prior Medications and Therapies

Frequency counts and percentages will be provided to summarize the classes of prior medications and therapies recorded on the eCRF.

8.6 Analysis of Efficacy Parameters

8.6.3 Change in lesion size

Change from baseline and percentage change from baseline in lesion size will be summarized with descriptive statistics for each follow-up visit. This will be done separately for greatest trans-axial diameter and for lesion volume. A per-lesion and a per-patient analysis of change in lesion size will be provided.

Waterfall plots of the percentage change in the lesion size, as measured by greatest trans-axial diameter, will be given for each follow-up visit.

8.6.4 Post-cryoablation lesion recurrence with enhancement and lesion progression with enhancement

The number and percentage of patients with post-cryoablation lesion recurrence with enhancement, and the number and percentage of patients with post-cryoablation lesion progression with enhancement, (as defined in Section 6.4.2) will be given for each follow-up visit. The percentage will be based on the number of patients who remain in follow-up at that visit (i.e. excluding patients who have withdrawn, died or completed after the end date of the analysis window). For example, if a patient withdrew from the study or died within the 36 month analysis visit window, the patient would be included in the 36 month visit percentage calculation, but would not be included in the percentage calculations for subsequent visits.

This analysis will also be performed for the following subgroups:

- NS complexity categories at baseline
- Procedure method
- Lesion size at baseline, by greatest trans-axial diameter, as categories of ≤4cm and >4 cm
- Comorbidities (human immunodeficiency virus [HIV]/immunocompromised; diabetes; hypertension; obesity; blood clotting disorder; abdominal surgery; cardiovascular; retroperitoneal surgery; von Hippel-Lindau; cancer, other than renal)
- Patients who did and did not receive subsequent cryoablation (note: these patients will need to be identified manually from the response to the 'Specify type of local or systemic therapy' field on the 'Follow-up/Further cancer therapy' eCRF page)
- Area suspicious for lesion recurrence (yes, no) (as defined in Section 6.4.1) at the same post-cryoablation visit
- Baseline lesion classification (i.e., exophytic, mesophytic, endophytic)

A statistical comparison between post-cryoablation lesion recurrence with enhancement (yes, no) based on the lesion status and area suspicious for lesion recurrence (yes, no) based on the Hounsfield units will be performed using Fisher's exact test separately for each post-cryoablation visit.

8.6.5 Post-cryoablation biopsy

The number and percentage of patients with a "Yes" response (as defined in Section 6.4.3) will be given. A 95% CI for the percentage will be computed using the method of Wilson (1927).

8.6.6 Analysis of Time-to-Event Endpoints

Rates will be derived from the Kaplan-Meier estimates; 6, 12, 24, 36, 48 and 60 month rates will be presented, together with 95% CIs computed using the log-log transformation methodology of Kalbfleisch and Prentice (1980). Quartiles will be presented and 95% CIs will be calculated on the quartiles using the methodology of Brookmeyer and Crowley (1982) using the log-log standard error. Plots of the Kaplan-Meier curve will be provided showing the number of patients at risk at the date of treatment (i.e., 0 months), and at 6, 12, 24, 36, 48 and 60 months after treatment.

8.6.6.1 Time to Recurrence (TTR)

TTR will be computed as

TTR (Months) = (Date of event/censor – Date of cryoprocedure +1)/ 30.4375.

Censoring will be performed in the following order:

1) If a patient does not have a baseline lesion assessment, then the TTR time will be censored at the date of cryoprocedure, regardless of whether or not recurrence was observed after treatment.
2) If a patient has recurrence but has two or more missing lesion assessment visits (according to the 6 to 60 month analysis visits in Section 6.2.2) immediately before recurrence was observed, the TTR time will be censored at the date of the post treatment lesion assessment that occurred immediately before the first of the missed visits. For example, if a patient had a lesion assessment at Month 6, but did not have an assessment at Months 12 and 24, and then had recurrence at the Month 36 asssessment, then the TTR time would be censored at the date of the Month 6 assessment.
3) If a patient is known not to have recurrence , the TTR time will be censored at the last date of lesion assessment date, or at the date of cryoprocedure if the patient does not have any post-treatment lesion assessments.

8.6.6.2 Disease-specific Survival (DSS)

DSS will be computed as

DSS (Months) = (Date of event/censor – Date of cryoprocedure +1)/ 30.4375.

For each patient that has not died due to kidney cancer, DSS will be censored at the date of death due to other causes or at the date last known to be alive as recorded on the eCRF.

8.6.6.3 Overall survival

OS will be computed as

OS (Months) = (Date of death/censor – Date of cryoprocedure +1)/ 30.4375.

For each patient that has not known to have died, OS will be censored at the date last known to be alive as recorded on the eCRF.

8.6.7 Analysis of Quality of Life Questionnaire (SF-12)

Change from baseline and percentage change from baseline for the ten SF-12 scores listed in Section 6.4.7 will be separately summarized for the 6 and 12 month timepoints by descriptive statistics. The analysis will also be performed separately by laparoscopic and percutaneous procedure methods.

8.6.8 Development of metastatic disease

The number and percentage of patients who developed metastatic disease will be given. A 95% CI for the percentage will be computed using the method of Wilson (1927).

The duration (months) between date of cryoprocedure and date of development of metastatic disease will be computed as

(Date of development of metastatic disease – Date of cryoprocedure +1)/ 30.4375,

and will be summarized with descriptive statistics.

8.6.9 Additional efficacy assessments

8.6.9.1 Lesion status

Lesion status (i.e., responses to the question "What is the status of the lesion?" in the follow-up lesion assessment eCRF page), will be summarized separately for each follow-up visit, as count and percentage in a per-lesion analysis. The number and percentage of lesions for each category will be given, together with a 95% CI based on Wilson (1927).

This analysis will also be performed separately

- For patients with <3 freeze cycles and <3 thaw cycles
- By procedure method (laparoscopic and percutaneous)
- By procedure method (laparoscopic and percutaneous) in patients with <3 freeze cycles and <3 thaw cycles
- By needle type (Needles with the cautery feature [IceRod CX, IceFORCE 2.1 CX, and IcePearl 2.1 CX] vs other types)

The following baseline results will be provided for lesions with a status of 'No longer present" at any follow-up visit:

- Number and percentage of lesions that are cystic or solid at baseline
- Baseline lesion size, by greatest trans-axial diameter, will be summarized with descriptive statistics and also as categories of ≤4cm and >4 cm
- Number and percentage in each frozen section pathology result category at baseline
- Number and percentage in each permanent section pathology result category at baseline

8.6.10 Assessment of Poolability

Since this is a multi-center study, analysis will be performed by pooling data across study sites. It is expected that data will be poolable across study sites since all sites and investigators will follow a common protocol with identical inclusion/exclusion criteria (same population), treatment, and outcome assessment. Therefore a statistical assessment of poolability is not planned.

8.7 Analysis of Safety

Safety analyses will be performed on both the ITT and RCC populations. The procedural and intra-operative data will be given for both the ITT and RCC populations.

8.7.1 Procedural and intra-operative data

The following procedural and intra-operative data will be summarized using descriptive statistics, or as a number and percentage for categorical data.

The following data will be summarized in a per-patient analysis:

- Procedure method (open, laparoscopic, percutaneous); this data will also be summarized by site, and also by NS complexity categories at baseline
- Surgical approach type (not applicable, transperitoneal, retroperitoneal, hand-assisted, single port, natural orifice transluminal endoscopic surgery [NOTES], other)
- Type of Galil Medical cryoablation system used (SeedNet, Presice, Visual-Ice)
- Method of monitoring used to place cryoablation needles (CT, MRI, ultrasound)
- Method of monitoring iceball formation (CT, MRI, ultrasound)
- Completion of cryotherapy (yes, no)
- Achievement of technical success at first post-cryoablation imaging assessment (yes, no)
- Who performed the procedure? (interventional radiologist [IR], urologist, IR and urologist together, other); this data will also be summarized by site
- Type of anesthesia used (general, regional, local only, conscious); this data will also be summarized by site
- Total anesthesia time (in minutes)
- Estimated blood loss during procedure (in cc)
- Total duration of operation (in minutes); this data will also be summarized by NS complexity categories at baseline
- Type of hemostatic agents or maneuvers used (none, compression, suturing, Floseal, Gelfoam, Surgicel, other)
- Number of lesions identified at baseline but not treated with cryoablation (categorical)
    - Note: the data should only be taken from the first (date) Follow-up Lesion Assessment for each subject
- Number of lesions treated with cryoablation (categorical)
- Number of freeze and thaw cycles; this data will also be summarized by NS complexity categories at baseline
- Involvement of the kidney's collecting system, according to the following fields on the eCRF:
    - Did the iceball appear to touch the collection system? (yes, no)
    - Did the iceball appear to involve (engulf) the collection system? (yes, no)
    - Was there evidence for new gross hematuria during the course of the procedure potentially due to involvement of the iceball with the collecting system? (yes, no)
- Post-operative hematocrit (in %)

- Time from initial diagnosis of the suspicious renal mass to the date of cryoprocedure (in months)
- Length of hospital stay (in hours)
- Surgical procedures performed during the patient's hospital stay? (yes, no)
- Extended hospital stay needed due to an adjunct procedure? (yes, no)
- Conversion to another surgical approach? (yes, no)
- Narcotics required post-op? (yes, no)

The following data will be summarized in a per-lesion analysis:

- Lesion in right or left kidney (right, left)
- Was embolization performed prior to cryoblation? (yes, no)
- Number and type of cryosurgery needles used; this data will also be summarized by NS complexity categories at baseline
- Hilar clamping performed? (yes, no)
- Use of thermal sensors (yes, no)
- Additional ablation cycles required on lesion? (yes, no)

The following data will be summarized in a per-cycle analysis:

- Freeze time (in minutes) within a cycle
- Thaw times (in minutes) within a cycle
- Lowest temperature achieved at end of each freeze cycle, separately for temperature at the center and at the periphery
- Method of thaw (active, passive)

The following will also be summarized in a per-lesion analysis:

- Total freeze times (in minutes) over all cycles
- Total thaw times (in minutes) over all cycles
- Lowest temperature achieved at end of all freeze cycle, separately for temperature at the center and at the periphery

8.7.2 Adverse Events

The number and percentage of patients with the following complications will be given, together with 95% CIs for the percentages, computed using the method of Wilson (1927):

- Intra-operative device complication
- Intra-operative device complication related to the malfunction of the cryoablation system cryosurgery
- Intra-operative patient complication

AEs will be summarized by the code list provided in the eCRF in descending order of frequency; a patient will only be counted once per code. Patient counts and percentages (and 95% CIs) and event counts will be presented for the following summaries.

- Overall summary of AEs, including
  - total number of AEs, SAEs, UADEs
  - total number of AEs, SAEs, UADEs by the following subgroups:
    - CTCAE grade
    - Clavien classification
    - Site
    - Procedure method
    - NS complexity category at baseline (as defined in Section 6.3)
    - ASA score
    - Baseline lesion classification (i.e., exophytic, mesophytic, endophytic); AEs for patients with multiple lesions with different classifications will be in a separate category.
    - Did iceball appear to touch the collection system?
    - Comorbidities (HIV/immunocompromised; diabetes; hypertension; obesity; blood clotting disorder; abdominal surgery; cardiovascular; retroperitoneal surgery; von Hippel-Lindau; cancer, other than renal)
- All AEs
- All AEs by CTCAE grade
- All AEs by baseline lesion classification (i.e., exophytic, mesophytic, endophytic); AEs for patients with multiple lesions with different classifications will be in a separate category
- All AEs by the comorbidities listed above
- All SAEs
- All UADEs
- All AEs with CTCAE grade ≥3
- All fatal AEs (CTCAE grade 5).

8.8 Other Analyses

8.8.1 Post-treatment lesion characteristics

The analyses described in this section will be performed on the ITT and RCC populations.

The following lesion characteristics will be summarized in a per-patient summary, separately for each post treatment visit:

- Duration (months) between date of cryoprocedure and date of imaging will be summarized with descriptive statistics
- The type of imaging used (CT, MRI, ultrasound)
- Number of new lesions identified which were not present at baseline
  - Number of new lesions that are ipsilateral
  - Number of new lesions that are contralateral

The following lesion characteristics will be summarized in a per-lesion summary, separately for each post treatment visit (i.e., over the total number of lesions recorded in the study for descriptive statistics, and as a percentage of the total number of lesions for categorical data):

- Lesion in right or left kidney (right, left)
- Lesion size, by greatest trans-axial diameter, will be summarized with descriptive statistics and also as categories of ≤4cm and >4 cm
- Lesion volume will be summarized with descriptive statistics
- The type of imaging used (CT, MRI, ultrasound)
- Lesion location
- Lesion classification
- Lesion shape
- Cystic or solid lesion
- Hounsfield units, separately for each of following phases
    - Non-contrast
    - Arterial Phase
    - Venous Phase
    - Delayed Phase
- Area suspicious for lesion recurrence according to Hounsfield units (as defined in Section 6.4.1)
- Biopsy performed?
- Duration (months) between date of cryoprocedure and date of biopsy sample will be summarized with descriptive statistics
- Type of biopsy
- If a core biopsy was performed, number of cores taken
- Frozen section pathology result
- Frozen section pathology classification
- Permanent section pathology result
- Permanent section pathology classification
- Fuhrman classification grade

8.8.2 New therapies for renal cancer

The analyses described in this section will be performed on the ITT and RCC populations, separately for each visit.

The following will be summarized by the number and percentage of patients:

- Disease free status
- Patients who received a new therapy for renal cancer
- Patients who received local and systemic therapy

- Patients who received subsequent cryoablation (note: these patients will need to be identified manually from the response to the 'Specify type of local or systemic therapy' field on the 'Follow-up/Further cancer therapy' eCRF page)

Duration (months) between date of cryoprocedure and date of new local therapy will be summarized with descriptive statistics. Also, the duration (months) between dates of first and subsequent cryoprocedures (retreatments) will be summarized.

8.8.3 Comparison of investigator and non-investigator imaging results

The analyses described in this section will be performed on the ITT population.

The agreement between investigator and non-investigator assessed lesion sizes will be assessed using Bland-Altman analysis (Bland, 1986) of the per-patient analysis lesion measurements (described in Section 6.4.1). This will include calculation of the 95% limits of agreement. This analysis will be performed for the largest lesion measurement (i.e., largest of AP, TR, CC, and greatest trans-axial diameter), separately for each visit (including baseline).

Agreement in the lesion classification (exophytic, meophytic or endophytic), will be assessed using Cohen's kappa coefficient (Cohen, 1960), and interpreted according to Landis and Koch (1977).

8.8.4 Renal function status

The analyses described in this section will be performed on the ITT and RCC populations.

The change from baseline in eGFR and sCR will be summarized using descriptive statistics for each follow-up visit. The change from baseline in CKD stage will be summarized in a shift table.

9 COMPUTER SOFTWARE

All analyses will be performed by BTG using Version 9.4 or later of SAS® software. All summary tables and data listings will be prepared utilizing SAS® software.

10 REFERENCES

Bland JM, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;327:307–310.

Brookmeyer, R and Crowley, J. A Confidence Interval for the Median Survival Time. Biometrics 1982;38:29–41.

Ceriotti F, Boyd JC, Klein G, Henny J, Queralto J, Kairisto V, Panteghini M. Reference intervals for serum creatinine concentrations: assessment of available data for global applications. Clin Chem. 2008;54:559-560.

Cohen J. A coefficient of agreement for nominal scales. Educ Psychol Meas 1960;20:37–46.

Kalbfleisch, JD and Prentice, RL. The Statistical Analysis of Failure Time Data. 1980. New York: John Wiley & Sons.

Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. J Urol. 2009;182:844–853.

Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–174.

Wilson, EB. Probable Inference, the Law of Succession, and Statistical Inference. Journal of the American Statistical Association 1927;22:209–212.

11 APPENDICES

11.1 APPENDIX 1: VARIABLE DEFINITIONS

Age will be calculated as follows

Age= (Cryoprocedure Date – Date of birth)/365.25.

Only the integer part of the result will be taken.

11.2 APPENDIX 2: STATISTICAL ANALYSIS AND PROGRAMMING DETAILS

The SAS procedure LIFETEST will be used in the Kaplan-Meier analyses. Patients who did not have an event will be censored.

Example code is as follows:

```
proc lifetest data=all method=km alpha=0.05 outsurv=interval;
  time aval*censr(1);
  id usubjid;
run;
```

The SAS procedure PHREG will be used in the Cox regression analysis of time-to-event endpoints. Patients who did not have an event will be censored. The SAS method of discrete will be used to handle ties.

Example code is as follows:

```
proc phreg data=all;
   model aval*censr(0) = &covar  /ties=discrete rl alpha=0.05;
run;
```

12 TABLE, LISTING, AND FIGURE SHELLS WILL BE PROVIDED AS A SEPARATE DOCUMENT.