

Protocol Signature Page



PROTOCOL TITLE: Multi-center Study of Metastatic Lung Tumors Targeted by
Interventional Cryoablation Evaluation (SOLSTICE)
PROTOCOL NUMBER: CUC13-LNG079
PROTOCOL VERSION: 02
PHASE: II
DATE: 3 FEB 2014

Galil Protocol Approval

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

Signature

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 study as described in the protocol.

Printed Name

Signature

Date

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SPONSOR: Galil Medical
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Table of Contents

1	<i>INTRODUCTION</i>	6
1.1.	History of Cryotherapy	6
1.2.	Metastatic Lung Cancer Treatment Options	7
2	<i>DEVICE DESCRIPTION</i>	7
3	<i>CLINICAL BACKGROUND</i>	8
3.1.	Cryoablation in the Treatment of Metastatic Lung Tumors	8
3.2.	Previous Clinical Studies Leading Up to and Supporting the Proposed Research	8
3.3.	Rationale Behind the Proposed Research	10
4	<i>STUDY OBJECTIVE</i>	10
4.1.	Study Objective	10
5	<i>STUDY DESIGN</i>	10
5.1.	Primary Endpoint	10
5.2.	Safety Data	10
5.3.	Other Data to be Assessed	11
5.4.	Baseline Index Tumor Characteristics	11
5.5.	Physical Function	11
5.6.	Quality of Life	11
5.7.	Risks	12
5.8.	Potential Benefits	12
6	<i>PATIENT POPULATION</i>	12
6.1.	Patient Selection	12
6.2.	Inclusion Criteria	12
6.3.	Exclusion Criteria	13
7	<i>STUDY PROCEDURES</i>	14
7.1.	Patient Enrollment	15
7.2.	Screening	15
7.3.	Cryoablation	15
7.3.1.	Treatment of Multiple Metastatic Lung Tumors	15
7.3.2.	Cryoablation Procedure	15
7.4.	Week 1 – Follow-up	17
7.5.	Month 1 – Follow-up	17
7.6.	Month 3 – Follow-up	18
7.7.	Months 6, 12, 18 and 24 – Follow-up	18
7.8.	Repeat Cryoablation Treatment(s) or Alternative Additional Treatment	18

7.9.	Study Completion or Withdrawal	19
7.10.	Pertinent Concurrent Medications	19
8	ASSESSMENTS	20
8.1.	Demographics	20
8.2.	Targeted Medical History	20
8.3.	Laboratory Tests	20
8.3.1.	Biopsy	20
8.4.	Physical Performance	20
8.5.	Quality of Life	21
8.6.	Imaging	21
8.7.	Response Determination	21
9	MANUFACTURING, HANDLING AND ACCOUNTABILITY OF STUDY DEVICE AND SUPPLIES	22
9.1.	Manufacturing, Packaging and Labeling	22
9.2.	Handling and Storage	22
9.3.	Study Supplies	22
9.4.	Recall of Investigational Device	22
10	STATISTICAL ANALYSIS	23
10.1.	Study Design and Sample Size Calculation	23
10.2.	Missing Data	24
10.3.	Analysis Populations	24
10.4.	Poolability	24
10.5.	Analysis	24
11	DATA MANAGEMENT	26
11.1.	Data Collection	26
11.2.	Data Processing	26
12	MONITORING PROCEDURES	27
12.1.	Monitoring and Auditing	27
13	SAFETY ASSESSMENTS	27
13.1.	List of Definitions	27
13.2.	Causality Assessment	28
13.3.	Recording and Reporting SAEs and UADEs	29
14	PRODUCT COMPLAINTS	30
15	INVESTIGATOR REQUIREMENT	30
15.1.	Study Initiation	30

15.2.	Informed Consent Form	30
15.3.	Institutional Review Board/Independent Ethics Committee	31
15.4.	Protocol Amendments	31
15.5.	Record Retention	31
16	STUDY COMMITTEE	31
16.1.	Medical Monitor	31
16.2.	Central Imaging Review	31
17	STUDY ADMINISTRATION	32
17.1.	Study Registration	32
17.2.	Study Discontinuation	32
17.3.	Discontinuation of a Study Site	32
18	CONFIDENTIALITY/PUBLICATION OF STUDY RESULTS	32
19	STUDY COMPLETION	33
20	PROTOCOL DEVIATIONS AND EXCEPTIONS	33
21	REFERENCES	34
22	APPENDIX A: ABBREVIATIONS	37
23	APPENDIX B: ANTICIPATED ADVERSE EVENTS AND CTCAE TERMS	38
24	APPENDIX C: KARNOFSKY PERFORMANCE STATUS (KPS)	41
25	APPENDIX D: ASA Physical Status Classification System	42
26	APPENDIX E: QUALITY OF LIFE (SF-12)	43

Table of Tables

Table 1: Schedule of Study Events.....	14
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1. INTRODUCTION

1.1. History of Cryotherapy

Cryotherapy (or cryoablation) 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 cancer, renal cancer, liver cancer, soft tissue cancer, fibroadenoma of breast, ear-nose and throat applications, pulmonary cancer, cryoanalgesia, dermatology, as well as pre-cancerous tumors of the cervix. Galil Medical has developed a range of products based on its cryotherapy platform and incorporating updated freezing technology and needle design.

Applying cold energy to human tissues is a well-known technique for treating various tumors as an alternative to surgery.¹⁻¹¹ The first modern physician to utilize this technique was James Arnott (England, 1865). Since Arnott's first experience, many trials have been conducted utilizing various techniques and devices.^{8,10} These have included pre-cooled metal blocks, pre-cooled needles,^{11,12} dry ice applications, spray/pour freezing with compressed or liquefied gases,^{12,13} refrigeration systems, thermoelectric methods and cryogenic heat pipes,¹⁴ cryogenic needles,¹⁵ Joule-Thomson-effect-based cryoprobes,^{15,16} and boiling-effect-based cryoprobes.¹³ To increase the effectiveness of the cryo-treatment, the freezing protocols used by these physicians were adjusted with the known maximal cryo-destruction criteria such as extremely fast cooling,⁹ low cooling rate at the freezing front,¹⁹ slow thawing,²⁰ and repeated freeze/thaw cycles.¹⁴

As tissue temperatures fall, extracellular water begins to crystallize and a hyperosmotic extracellular environment is created that draws water out of the cells. As the process continues, extracellular ice crystals grow, cells shrink, and membranes and cell constituents are severely damaged. Within a short time (minutes), the increased extracellular electrolyte concentration is sufficient to destroy the cells. This effect of cell dehydration and solution concentration, called solution-effect injury, is not always lethal to cells; on the other hand, intracellular ice formation is a more significant threat to cell viability and is almost always lethal.⁸ Solution-effect injury is associated with low freezing rates, while intracellular ice formation is commonly associated with fast freezing rates. Although pure water begins to freeze at 0°C, extracellular ice formation occurs at approximately -7°C to -10°C, by -15°C intracellular ice begins to form (heterogeneous nucleation). Depending on the tissue characteristics (e.g., vascularity, density, etc.) at -20°C to -40°C all metabolic processes are expected to have ceased (homogenous nucleation). The most destructive effect on biological tissue is achieved by either an extremely low temperature or a very rapid freezing rate (on the order of hundreds of degrees Centigrade per minute).^{8,9} More recent *in vitro* and *in vivo* work has identified apoptosis as the mechanism associated with direct cell injury. Cell death has been demonstrated in the central part of the ablation zone by evidence of coagulation, while apoptosis is evident generally 8-12 hours after cryoablation in the peripheral part of the lesion.¹⁷

Cryoablation is an advantageous therapy as it preserves collagenous and other cellular architecture in virtually any frozen tissue and offers the ability to see low attenuating ice as it covers soft tissue during the freezing cycle.¹⁸

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.⁵ 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 – 3,500 psi) ambient-temperature argon gas is circulated to the cryoablation needle 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 cryoablation needle 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 cryoablation needles 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 min.⁶⁻⁷ The expanded gases are circulated back to the cryogenic unit through the larger outer lumen of the cryoablation needle 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.

The cryoablation technology developed by Galil Medical (Arden Hills, MN) is based on Joule-Thomson effect, and utilizes Argon gas for freezing and Helium gas for thawing.

This study will utilize Galil Medical's commercially available Cryoablation System and needles. Each type of cryoablation needle forms a different shape and size of iceball. Multiple cryoablation needles may be inserted into the tumor, or even into multiple tumors concomitantly. This significantly shortens the length of treatment and provides flexibility in treating tumors of varying sizes by matching the cryoablation needle number and configuration for a specific tumor.

Cryoablation procedures using Galil Medical's Cryoablation Systems may be performed under the guidance of Ultrasound, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI).

1.2. Metastatic Lung Cancer Treatment Options

Common primary tumors that usually present as lung metastasis are breast, colon, kidney, uterus and cervix, prostate, and head and neck tumors.²¹ The choice of treatment depends on the patient's medical history, comorbidities and the number and size of the metastatic lung tumors, as well as the control of the disease distant from the lung, including primary tumor and potential metastases to other organs. The most classical treatment options may include surgery, chemotherapy, radiation therapy, or a combination of treatments.²² Many patients are not surgical candidates because of the extent of the disease. However among patients with a disease that theoretically could be amenable to surgical resection, some are not surgical candidates because of either their advanced age, or various comorbidities, including often poor cardiopulmonary function. For these high-surgical risk patients, external beam radiation has evolved as a local therapy option. The highest reported, two year overall survival rate is 51%. Percutaneous image guided tumor ablation in the lung has been used for over a decade as a local treatment, and routinely employed for metastatic lung tumors. The ablative technologies available for such treatment include radiofrequency, microwave and cryoablation.

Image guided thermal ablation has been adopted primarily by the radiology community, however other medical specialties are now adopting ablation in the care of their patients. Image guided thermal ablation offers a repeatable, effective, low-cost, and safe treatment either as the single mode of treatment or in combination with other therapies.^{36,37}

2. DEVICE DESCRIPTION

Galil Medical's Cryoablation Systems (Galil Medical, Arden Hills, MN) and needles are FDA cleared. The Galil Medical Cryoablation Systems are intended for cryogenic destruction of tissue during surgical procedures; various Galil Medical ancillary products are required to perform these procedures. Galil Medical Cryoablation Systems are indicated for use as a cryosurgical tool in the fields of general surgery, dermatology, neurology (including cryoanalgesia), thoracic surgery, 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. Tissue thermal sensors may be employed to enable the real-time tissue temperature monitoring, thus, contributing to the safety and effectiveness of the procedure.

3. CLINICAL BACKGROUND

3.1. Cryoablation in the Treatment of Metastatic Lung Tumors

Ablation of metastatic lung tumors is a rapidly expanding area within interventional oncology. Cryotherapy, radiofrequency, laser and microwave have all been shown to be effective.²³ Cryotherapy offers a wide range of anatomic and tumor treatment options because of the ability to visualize the ice under imaging guidance and the preservation of collagenous tissue structure. Cryoablation has been extensively performed in the prostate and kidney with favorable outcomes reported in the literature. More recently, cryoablation has been shown to be safe in the treatment of lung tumors with CT guidance.^{24,33,34,35}

3.2. Previous Clinical Studies Leading Up to and Supporting the Proposed Research

Inoue et al has reported on the safety and feasibility of percutaneous cryoablation for lung tumors. This study included 396 lung tumors in 117 (104 with metastatic disease) consecutive patients conducted in 193 cryoablation sessions. All patients tolerated the procedure well. The mean follow up period was 899± 778 days. Adverse events were categorized using the CTCAE system. Pneumothorax was the most common complication observed in 61.7% of the treatment sessions. Of these, 10.9% of the cases required chest tube insertion, comparable to that associated with RF ablation. Delayed and recurrent pneumothorax each occurred in 30 of the treatment sessions, resulting in 17 chest tube insertions. Risk factors predictive of pneumothorax were male sex, and greater number of cryoneedles. The authors theorize the higher pneumothorax rate may be related to the number of cryoneedles used, thicker modified coaxial system, and the modality used to detect pneumothorax. Pleural effusion occurred in 136 treatment sessions and required no additional treatment. No CTCAE grade 4 or 5 events were observed. Three grade 3 complications were noted; one in which an empyema required fenestration and 2 cases of pneumothorax which required pleurodesis. Inoue et al concluded that percutaneous cryoablation is minimally invasive and associated with improved safety.³²

Yamouchi et al reported the use of percutaneous cryoablation for pulmonary metastases from colorectal cancer on 24 patients for 55 tumors during 30 treatment sessions. Follow up scans were performed every 3-4 months after treatment. Pneumothorax was reported in 19 sessions with only 1 session requiring insertion of a chest tube. A small amount of pleural effusion occurred in 21 sessions, none of which required a chest tube. The 1- and 3-year local progression free intervals were 90.8% and 59%, respectively. The 1- and 3-year overall survival rates were 91% and 59.6%, respectively.³³

Kawamura et al reported a series of 35 tumors in 20 patients treated with cryoablation for metastatic pulmonary tumors. Criteria for treatment included tumors < 3cm, less than 5 metastatic tumors, life expectancy greater than 1 year, absence of active extrapulmonary metastasis, Eastern Cooperative Oncology Group scores of 0 to 1, definitive pathologic diagnosis or obvious clinical features, and normal coagulability. CT guided cryoablation was performed with a 2 or 3 mm diameter cryoprobe (Endocare, Inc.) with 2 cycles of 5 minute freezing followed by a third cycle of 10 minute freezing to make an iceball of 2.5 to 3.0 cm in diameter. Local anesthesia was used in all cases. The primary endpoint of this study was the early outcome and feasibility of cryoablation for metastatic tumors < 3 cm. The secondary endpoint was tumor control. The mean age of patients was 57 years old. Two of the 20 patients underwent cryoablation twice due to bilateral metastasis, resulting in a total of 22 cryoablation sessions. The mean hospital stay was 2.6 days. There were no treatment related deaths or conversion to surgical intervention. Response Evaluation Criteria in Solid Tumors (RECIST) was applied to assess change in tumor mass post-operatively. Two patients had complete response, 8 had partial response, 8 had stable disease, and 2 had progressive disease, thus resulting in a 50% response rate with 90% control rate. The overall tumor recurrence rate was 54.3%. The median follow-up was 21 months for 18 patients. During the 9-12 month period, 7 of the 18 (35%) patients

developed a local recurrence of 7 (20%) tumors. Five patients underwent additional cryoablation treatments without complication or local recurrence. Pneumothorax was reported in 50% of the cases, 27% experienced pleural effusion, 41% hemothorax, and 4.5% phrenic nerve palsy. The Kaplan Meier 1-year survival was 89.4%.²⁶

Wang et al reported a series of 187 patients who underwent CT guided percutaneous cryoablation for thoracic masses. The mean age of the patient population was 61 years. Primary lung cancer accounted for 84% of the tumors in 88% of the patients while metastasis was found in 12% of the patients. Percutaneous cryotherapy procedures were performed with 2 and 3mm cryoprobes (Endocare). A treatment cycle consisted of a 20 minute freeze, 10 minute thaw or increase in temperatures to 0-5° C, followed by another 20 minute freeze. A single cryotherapy session was performed in 178 (76%) patients. Repeat ablations were performed for larger central masses, multiple pulmonary masses, and bilateral masses. There were no intra-operative complications or technical difficulties. CT images were obtained immediately after the cryoablation procedure. The ice was well seen, however it was not possible to visualize the frozen tissue in the adjacent lung, and therefore only estimates of ice coverage of soft-tissue components of thoracic masses could be made. Tumor size and location were significant variables for determining the likelihood of tumor coverage with ice. Peripheral masses < 4 cm had mean ice coverage in 99% of the cases and 80% coverage were noted for central masses > 4cm. Two deaths occurred after the cryoablation. One patient died within 1 day due to a pulmonary embolus and the second a week after the procedure due to acute respiratory distress. Pneumothorax occurred on 12% of the procedures, pleural effusion in 14%, and hemoptysis 62%. The Karnofsky score improved significantly one week after the procedure. CT imaging after the cryoablation procedure was performed at 1 week, 3 month, 6 months and 12 months when possible. Authors emphasized the need for 1-cm ablative margins as treatment goals. By 6 months, 86% of the cases demonstrated involution or stability of the treatment site. Due to low follow-up, the calculation of accurate survival estimates was not possible.²⁷

Pusceddu et al reported on the use of percutaneous cryoablation in patients with primary and secondary lung tumors. All treatment sessions were successfully completed and no procedure related deaths occurred. CTCAE grade 1 pneumothorax was reported in 7 of 34 sessions (21%) and 1 occurrence of a CTCAE grade 1 pleural hemorrhage. All patients had a hospital stay of 24 hours or less. Comparison of the tumor longest diameter between baseline and 6 month CT images demonstrated technical success in 92% of cases ($p < .000$).³⁴

Asimakopoulos et al reported 5 year follow-up of a series of 172 patients (Group A) who underwent 2 cryoablation treatments and 157 patients (Group B) who underwent 1 cryoablation treatment for primary or metastatic obstructive lung disease. Subjects assigned to group A were able to complete the standard cryoablation protocol and subjects in group B were those only able to undergo 1 session of cryoablation. The primary outcome was to examine the effects of cryoablation on symptoms, lung function, and performance scores. Dyspnea was classified using the New York Health Association (NYHA) classification. Tumor stage at the time of cryoablation was determined to be stage IIIb or IV in 67% of group A and 77% in group B. Treatment was performed using a nitrous oxide cryoprobe (Spemby Medical, UK/Integra Life Sciences) which achieved a temperature of -70° C at the time of treatment. Treatment was applied to the tumor for two 3-minute freeze cycles. Ninety-five percent of the patients were discharged on the same day as the cryoablation procedure. Patients were scheduled for follow-up at 2 weeks and 8 weeks after the second session of cryotherapy. Complications reported after cryotherapy included bleeding in 3.5% of group A and 5% of group B, new onset of atrial fibrillation in 1.7% of group A and 3.8% of group B, and respiratory distress in 2.3% of group A and 5% in group B. Palliative or adjuvant treatment with radiotherapy, chemotherapy or resection was provided based on the tumor stage, histology, or patient preference. Squamous cell carcinoma was present in 66% of patients in group A and 63% of those in group B. Fifty seven percent of group A underwent palliative radiotherapy, 11% chemotherapy, and 7% resection. Twenty eight percent of group B underwent palliative radiotherapy, 11% chemotherapy, and 5% resection.

Dyspnea improved by at least one NYHA classification in 37% of subjects in group A and only in 11% of those in group B by their second follow-up. Cough improved in 43% of group A and 11% in group B and hemoptysis in 20% of group A and 4% of group B. Data was limited in group B due to the limited follow-up attendance. Lung function also increased significantly in group A at their first follow-up but the benefit was lost by their second visit. Patients in group B did not show improved lung function by their first follow-up visit. The mean survival after cryotherapy was 15 months in group A and 8.3 months in group B. Karnofsky score improved at least 10% in group A as well as in group B. The clinical benefit of cryoablation is primarily attributable to tumor debulking, achieved by the destruction of the endobronchial element of the tumor and recanalization of the tracheobronchial obstruction. The removal of this obstruction accounts for the improvement in dyspnea and lung function tests, which are vital to the alleviation of symptoms in those with lung cancer due to the poor prognosis of this disease.²⁵

3.3. Rationale Behind the Proposed Research

There are several different methods for treating pulmonary metastatic disease. Treatment may include surgery, chemotherapy, radiation therapy, or a combination of treatments. However, several variables may exclude patients from these treatments such as multiple tumors, multiple previous surgeries, pulmonary dysfunction, or co-morbid medical conditions.³³ For these patients, percutaneous cryoablation may be a suitable option.

The target population for this study is patients with pulmonary metastatic tumors who are candidates for cryoablation therapy. This study will evaluate the safety and efficacy of cryoablation therapy used to treat tumors in patients with pulmonary metastatic disease.

4. STUDY OBJECTIVE

4.1. Study Objective

The objective of this study is to assess the safety and to demonstrate efficacy of cryoablation in local tumor control for tumors ≤ 3.5 cm in patients with pulmonary metastatic disease.

5. STUDY DESIGN

This is a Phase II multicenter, prospective, single arm study. Target inclusion for this study is 226 tumors. It is estimated this study will enroll 150 patients across approximately 15 study sites in the United States and internationally in order to achieve the target tumor goal. Patients enrolled will undergo cryoablation of at least 1 metastatic pulmonary tumor via a Galil Medical cryoablation system using Galil Medical cryoablation needles.

Patients will be screened before the cryoablation procedure. After the cryoablation procedure, protocol directed follow-up visits will occur within 1 week of the cryoablation procedure and then 1, 3, 6, 12, 18, and 24 months post cryoablation procedure.

5.1. Primary Endpoint

The primary endpoint for this study is defined as follows:

- Efficacy of cryoablation on local tumor control for each index tumor in patients with pulmonary metastatic disease at 12 months post cryoablation. (See Section 8.7)

5.2. Safety Data

The safety data for this study will be assessed to report the incidence and severity of cryoablation related adverse events.

5.3. Other Data to be Assessed

Other data for this study include, but are not limited to:

- Overall patient survival post cryoablation;
- Time to metastatic lung disease progression beyond the index tumor(s);
- Time to overall cancer progression;
- Time to untreatable metastatic lung disease control with cryoablation;
- Time to untreatable metastatic lung disease control with focal therapy;
- Efficacy of cryoablation on local tumor control for each index tumor in patients with pulmonary metastatic disease at 18 and 24 months post cryoablation;
- Efficacy of cryoablation on local tumor control for each index tumor in patients with pulmonary metastatic disease undergoing additional cryoablation treatment(s) of a previously treated index tumor;
- Cryoablation technical success (See Section 10.5.5);
- Changes in physical function and quality of life over time (See Section 10.5.5).

5.4. Baseline Index Tumor Characteristics

The tumor(s) intended for ablation is referred to as the **index tumor(s)**. Index tumor characteristics will include, but are not limited to:

- Histology of primary tumor;
- Proof of metastases;
- Location of the index tumor(s) in the lung(s);
- Size of the index tumor(s);
- Number of index tumors.

5.5. Physical Function

Physical function is considered routine clinical practice in medicine. Specifically, in oncology practice, physical function assessments such as the Karnofsky Performance Scale (KPS) have been incorporated.

This study will use KPS to assess physical function.

5.6. Quality of Life

Oncology trial outcome measures appropriately focus on physical response to therapy and severe adverse events. However, over the past two decades, trial measurement has increasingly included the impact of therapy on the broader arena of quality of life, defined by a number of physical and psychosocial domains.^{29,30} The underlying concept is that quality of life may assist in distinguishing treatments that are otherwise similar in therapeutic value and toxicity. There has been some debate about the clinical usefulness of quality of life measures, but at least one recent report has documented their impact on clinical decision-making.³¹

This protocol will utilize the SF-12 generic measure. The SF-12 is a shortened version of the well-known SF-36. The SF-12 uses twelve items to assess eight domains (physical functioning, role limitations due to physical health problems, bodily pain, social functioning, general mental health, role limitations due to emotional problems, vitality, general health perception).³² The shorter instrument will provide a general measurement of quality of life.

5.7. Risks

Potential risks of pulmonary tumor cryoablation in the intra procedure/early post-procedure period include bleeding, cough, hemoptysis, fever, infection, hypertension, pleural effusion, pneumothorax, nerve or skin injury.

Potential delayed risks of pulmonary tumor cryoablation include pneumothorax, pulmonary embolus, infection, and other unlikely complications, including death.

5.8. Potential Benefits

Galil Medical's Cryoablation Systems (Galil Medical, Arden Hills, MN) and needles are FDA-cleared for the ablation of cancerous or malignant tissue and benign tumors, and palliative intervention. Potential benefits of pulmonary tumor cryoablation include improved performance status and local tumor control and may include palliative relief of symptoms associated with the disease including dyspnea, cough and hemoptysis.

6. PATIENT POPULATION

6.1. Patient Selection

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom cryoablation therapy is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether cryoablation therapy is suitable for a particular patient.

6.2. Inclusion Criteria

Eligible patients for this study must meet all of the following criteria:

- 6.2.1. Patient must be at least 18 years old.
- 6.2.2. Patient has signed a written informed consent.
- 6.2.3. Patient presents with Stage 4 pulmonary metastatic disease with metastatic disease previously confirmed by prior biopsy;
or
Patient presents with Stage 4 pulmonary metastatic disease previously confirmed on imaging (e.g. CT) with histology proven primary cancer.
- 6.2.4. Patient has up to 6 local pulmonary metastases targetable by cryoablation.
- 6.2.5. Targeted index tumor(s) defined as intra pulmonary or pleural with a maximum size of 3.5 cm, measured in the longest cross sectional dimension.
- 6.2.6. The target index tumor(s) is determined (by CT images) to be in a location where cryoablation is technically achievable based on the proximity of adjacent organs/ structures and is greater than 0.5 cm from any critical organ/structure (possibly achieved with additional maneuvers such as iatrogenic pneumothorax or hydrodissection).
- 6.2.7. Karnofsky Performance Scale (KPS) score ≥ 60 .
- 6.2.8. Platelet count $>50,000/\text{mm}^3$ within 8 weeks prior to initial cryoablation procedure.
- 6.2.9. INR <1.5 within 8 weeks prior to initial cryoablation procedure.
- 6.2.10. Patient has a life expectancy of >3 months.

6.3. Exclusion Criteria

Patients not eligible for participation in this study include patients who have any of the following:

- 6.3.1. Patient's index tumor(s) is primary lung cancer.
- 6.3.2. Patient has uncontrollable primary or metastatic disease outside of the lung.
- 6.3.3. Patient is unable to lie flat or has respiratory distress at rest.
- 6.3.4. Patient has a coagulopathy or bleeding disorder which is uncontrolled.
- 6.3.5. ANC <1000 within 8 weeks prior to initial cryoablation procedure.
- 6.3.6. Patient has evidence of active systemic, pulmonary, or pericardial infection.
- 6.3.7. Patient has a debilitating medical or psychiatric illness that would preclude giving informed consent or receiving optimal treatment or follow up.
- 6.3.8. Patient is currently participating in other experimental studies that could affect the primary endpoint (e.g. experimental chemotherapy regimen).

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7. STUDY PROCEDURES

The study schedule of events and the specific procedures performed at each visit are shown in Table 1, Schedule of Events. Each patient will undergo a total of 9 visits, including an initial/screening visit, the procedure visit, and 7 post-operative visits. More visits may be required when medically necessary.

Table 1: Schedule of Study Events

Procedures	Screening ^a	Procedure Date	W 1 ^c	M 1 ^e	M 3 ^{g,h,i}	M 6, 12, 18, 24 or W/D ^{g,h,i}
Informed Consent	X					
Inclusion/Exclusion	X					
Demographics	X					
Targeted Medical History	X					
Karnofsky Performance	X			X	X	X
Pertinent Medication	X		X	X		
Discontinue anticoagulation, as clinically indicated	X	X				
Imaging Scan	X ^f		X ^d	X ^f	X ^f	X ^f
Record index tumor characteristics	X					
Cryoablation procedure		X ^b				
Labs	X					
Quality of Life (SF-12)	X			X	X	
Safety Assessment		X	X	X	X	X

^a All screening visit requirements should be within 8 weeks of the initial cryoablation procedure. Any items (e.g., imaging or lab assessment) previously conducted as routine standard of care prior to the signed informed consent may be used to satisfy the screening requirements provided they are completed within 8 weeks of the initial cryoablation procedure.

^b If multiple tumors are planned for study inclusion, treatment of all study index tumors should be completed within an 8 week window.

^c The week 1 follow up visit may take place prior to discharge from the hospital or within 1 week (7 days) of the cryoablation procedure.

^d Week 1 imaging may be a chest CT ± contrast or chest X-Ray

^e Month 1 visit window 30 days -7/+21 days

^f Chest CT scan ± contrast (contrast is preferred)

^g Months 3, 6, 12, 18 and 24 visit window +/- 30 days

^h In the event of multiple cryoablation procedure dates, the most recent procedure date will serve as the reference for determining the follow up visit window.

ⁱ While return visits are preferred to be conducted in the clinic setting, in the event the patient is not able to return due to distance or illness, follow up assessments (i.e. all assessments with the exception of imaging) may be conducted via telephone or tele-video (e.g. Skype). Tele-video should only be considered if the patient has the knowledge and access to such technology.

7.1. Patient Enrollment

To minimize selection bias within the enrolled patient population, participation in the study is to be offered to all eligible patients on a consecutive basis as they present to the physician at the site. All eligible patients will be assigned a screening number. The screening log will include minimal health information regarding each non-enrolling patient (e.g., sex, age, reason for not enrolling, etc.). As the non-enrolled patients will not sign an informed consent form the data collected will not include personally identifiable information (as defined in 45 CFR 164.514).

Patients who wish to participate in this study and sign a written informed consent form will be assigned a unique identifier number at baseline to be used throughout the study.

7.2. Screening

The screening visit allows the investigator to assess a patient's eligibility for this study.

The following assessments will be used to support patient enrollment and shall be performed within 8 weeks of the initial cryoablation procedure. Any items (e.g., imaging or lab assessment) previously conducted as routine standard of care prior to the signed informed consent may be used to satisfy the screening requirements provided they are within 8 weeks of the initial cryoablation procedure.

- Informed consent;
- Review inclusion/exclusion criteria;
- Patient number assigned;
- Demography;
- Targeted medical history, including comorbidities;
- Karnofsky Performance Scale;
- Baseline labs (Platelet Count, ANC and INR);
- CT scan of chest ± contrast (contrast is preferred);
- Baseline index tumor characteristics (See Section 5.4);
- Quality of Life assessment (SF-12);
- Current pertinent concomitant medication;
- Discontinue anticoagulation as clinically indicated;

7.3. Cryoablation

7.3.1. Treatment of Multiple Metastatic Lung Tumors

Treatment of all study index tumors should be completed within an 8 week window. Tumors contained in both lungs should be treated in an appropriate interval determined on an individual basis. It is not recommended that bilateral index tumors be treated in a single treatment session.

7.3.2. Cryoablation Procedure

For cryoablation, patient preparation, anesthesia, intra-operative monitoring, and post-operative management are identical to those of standard cryoablation treatments routinely performed at all clinical centers participating in this study and are at the discretion of the investigator.

Galil Medical's Cryoablation System will be used per the manufacturer's guidelines. Galil Medical's cryoablation needles will be placed under CT image guidance in a pattern necessary to fully freeze the target tumor(s). The treatment will be administered utilizing cryoablation needles with

compressed argon gas through the Joule-Thomson effect to produce extremely low temperatures within the target tumor(s).

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

- ASA Physician Status Classification (Appendix E)
- Number of tumors treated with cryoablation;
- Index tumor size measurement:
 - 3 axes of measurements (cm) (largest diameter and two perpendicular diameters)
- Number and type of cryoablation needles used;
- Number of freeze and thaw cycles;
- Freeze and thaw times, per cycle;
- Number and type of intra-operative complication(s)
 - Severity of complication(s);
- Length of hospital stay;
- Total procedure time;
- Anesthesia type;
- Additional surgical intervention(s);
- Safety assessment.

7.3.3. Cryoablation needle placement

The number and configuration of the needles will be based on the necessity to maintain appropriate distances between adjacent cryoablation needles and anatomic structures, and the final number of needles can only be formulated based upon the configuration of the index tumor(s) at the time of treatment. The use of a single needle per tumor should be avoided as it is well understood there is a benefit to multiple needles as a result of ice coalescence and the potential for increased risk of recurrence. The CT imaging views of the index tumor(s) will enable final assessment of the percutaneous access route and needle placement on the day of the procedure. Cryoablation needles will be placed to create multiple overlapping iceballs to completely cover the index tumor and provide a 5 mm zone of ablation surrounding the index tumor while maintaining appropriate safe distance from the non-targeted tissues (i.e. main bronchus and pulmonary arteries).

7.3.4. Cryoablation needle testing

Before anesthesia inducement of the patient, all cryoablation needles should be tested in accordance with Galil Medical's Cryoablation System User Manual to confirm their freezing function and structural integrity.

7.3.5. Freezing procedure

Once freezing has been initiated, the cryoablation procedure will be monitored with CT ± contrast imaging to visualize iceball growth, to ensure the ablation zone is adequately frozen and adjacent anatomical structures are protected. As the freezing continues, the ice formation from each of the cryoablation needles coalesce so the targeted portions of the ablation zone are frozen.

The guideline for pulmonary cryoablation is typically 3 freeze/thaw cycles. The following three cycle freeze-thaw protocol is suggested to be employed:

- Cycle 1: Freeze 3 minutes followed by passive thaw for 3 minutes;
- Cycle 2: Freeze 7-12 minutes followed by passive thaw for 3 minutes;
- Cycle 3: Freeze 7-12 minutes followed by active thaw in order to aid in the removal of the cryoablation needles.

7.3.6. Procedure completion

CT images are typically obtained in the transverse and longitudinal planes showing the greatest extent of freeze. The ice should encompass the entire tumor extending beyond the tumor margin in all dimensions with a goal of >5mm. After cryoablation needle removal, CT images will be obtained to assess any bleeding or pneumothorax development. If any adverse event is diagnosed it should be managed per standard of care.

An antibiotic of choice can be prescribed if needed according to center preferences in order to prevent post-operative infection.

7.4. Week 1 – Follow-up

The week 1 follow up visit may take place prior to discharge from the hospital or within 1 week (7 days) of the cryoablation procedure. Patients are to complete the following assessment:

- Chest X-Ray or chest CT scan \pm contrast (contrast is preferred) to identify possible post-procedure adverse events (may be assessed by last CT scan of the cryoablation procedure);
- Safety assessment;
- Current pertinent concomitant medication.

7.5. Month 1 – Follow-up

Patients will return 1 month (30 days $-7/+21$) post cryoablation procedure. In the event of multiple cryoablation procedure dates, the most recent procedure date will serve as the reference for determining the follow up visit window.

The following assessments will be completed:

- Quality of Life assessment (SF-12);
- Karnofsky Performance Scale;
- Safety assessment;
- Chest CT scan \pm contrast (contrast is preferred) to identify possible post-procedure adverse events. This 1 month imaging will serve as the new baseline for tumor response evaluation;
- Assessment of metastatic lung disease progression beyond the index tumor(s) and feasibility of treatment;
- Assessment of local tumor recurrence at the index tumor, including additional treatment and feasibility of treatment;
- Assessment of any systemic cancer treatment(s);
- Assessment of any local therapy for the index tumor(s).
- Current pertinent concomitant medication.

7.6. Month 3 – Follow-up

Patients will return at 3 months (+/-30 days) post cryoablation procedure. In the event of multiple cryoablation procedure dates, the most recent procedure date will serve as the reference for determining the follow up visit window.

The following assessments will be completed:

- Quality of Life assessment (SF-12);
- Karnofsky Performance Scale;
- Chest CT scan \pm contrast (contrast is preferred);
- Safety assessment;
- Assessment of metastatic lung disease progression beyond the index tumor(s) and feasibility of treatment;
- Assessment of local tumor recurrence at the index tumor, including additional treatment and feasibility of treatment;
- Assessment of any systemic cancer treatment(s);
- Assessment of any local therapy for the index tumor(s).

7.7. Months 6, 12, 18 and 24 – Follow-up

Patients will return 6, 12, 18, and 24 months (+/-30 days) post cryoablation procedure. In the event of multiple cryoablation procedure dates, the most recent procedure date will serve as the reference for determining the follow up visit window.

The following assessments will be completed:

- Karnofsky Performance Scale;
- Chest CT scan \pm contrast (contrast is preferred);
- Safety assessment;
- Assessment of metastatic lung disease progression beyond the index tumor and feasibility of treatment;
- Assessment of local tumor recurrence at the index tumor, including additional treatment and feasibility of treatment;
- Assessment of any systemic cancer treatment(s);
- Assessment of any local therapy for the index tumor(s).

7.8. Repeat Cryoablation Treatment(s) or Alternative Additional Treatment

Patients may receive additional cryoablation treatment(s) to the index tumor(s) initially subjected to cryoablation while participating in the study protocol. This additional cryoablation may be performed on the index tumor(s) provided that the additional treatment is performed with Galil Medical technology. In this situation, for each index lesion retreated, follow-up visits will restart per the study protocol and continue through the 24 month visit after the date of the repeat cryoablation treatment. When possible, if multiple tumors are present, all efforts should be made to align all follow up visits. For any index lesion not subjected to retreatment, the data collection continues per protocol.

- Baseline labs are recommended to be repeated prior to any repeat cryoablation procedure;
- It is recommended to discontinue anticoagulation as clinically indicated;

- SF-12 will not be collected prior to or after any repeat cryoablation of index tumor(s);
- Pertinent medications should be reviewed prior to and after any repeat cryoablation of index tumor(s);
- All other follow-up requirements are still applicable.

If other local treatment (e.g. radiofrequency ablation, microwave ablation, surgery, radiation) is used on the index tumor(s) initially treated, then the patient must be withdrawn from the study.

Data will be collected regarding any systemic cancer therapy the patients receive during the course of the study.

7.9. Study Completion or Withdrawal

Patients may withdraw from this study at any time, with or without a reason, without prejudice to further treatment. Investigators should make every effort within the bounds of safety and patient choice to have each patient complete the study. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal; request the patient return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events. If possible, the reason(s) for withdrawal (if given) will be recorded.

If the patient withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Patients who request Early Termination from the study will be asked to return if physically capable for a final visit to complete the following assessments.

- Karnofsky Performance Scale;
- Chest CT scan, \pm contrast (contrast is preferred);
- Safety assessment;
- Assessment of metastatic lung disease progression, including additional treatment;
- Assessment of any new cancer treatment(s).

In the event the patient enters hospice or another similar care program, early termination should be documented. Information taken from the medical record is sufficient to document this reason for early termination in the event this communication is not provided by the patient.

Patients may be considered "lost to follow-up" after 3 unsuccessful attempts to contact the patient with one contact being a registered letter to the last known address of the patient. Site should document all attempts to contact the patient in the source documents.

7.10. Pertinent Concurrent Medications

Data will be collected regarding concurrent pertinent medication taken at the time of screening and through 30 days post procedure. In the event of multiple cryoablation procedures, the pertinent medications will be followed through 30 days of the last procedure. Any medication which could affect the outcomes of this study should be included. Examples of pertinent medication include any medication taken for the following indications:

- Treatment of cancerous tumors within the lung;
- Improve/affect lung function (including cough);

- Anticoagulation therapy;
- Antiplatelet therapy.

Medications recorded at screening which are prescribed for coagulopathy or bleeding disorders must appropriately wash out before the cryoablation procedure according to the investigator's standard of care. These medications include, but are not limited to, warfarin (e.g. Coumadin), clopidogrel (e.g. Plavix), Phenindione (e.g. Dindevan) and aspirin. Herbal supplements with blood thinning properties should also be washed out appropriately.

Supplemental treatment which, in the investigator's opinion, becomes necessary during the course of the study must not be denied to the patient. If this supplemental treatment is described as a therapy expressly not permitted or which may affect the primary efficacy outcome, the patient's participation in the study will need to be discontinued due to non-permitted concurrent therapy.

8. ASSESSMENTS

8.1. Demographics

Demographic information will be collected from the patient during screening. The information will consist of age at the date of consent, race and sex. Per French regulations, race and ethnicity will not be collected at any study site in France.

8.2. Targeted Medical History

Targeted medical history information must be obtained from each patient entering the study. Obtaining accurate medical history is necessary to ensure documented baseline health status and to ensure that patients meet study entry criteria.

8.3. Laboratory Tests

Laboratory tests will be performed by the site's local laboratory. The following laboratory tests are required within 8 weeks of the initial cryoablation procedure.

- Platelet Count;
- ANC;
- INR.

8.3.1. Biopsy

A biopsy of a tumor(s) in the lung(s) metastasized from another primary disease may be obtained at the discretion of the treating investigator per his/her standard practice.

8.4. Physical Performance

Physical function assessments will be measured using Karnofsky Performance Scale (KPS).

Karnofsky Performance Scale (KPS)

The Karnofsky Performance Scale is a standard way of measuring the ability of cancer patients to perform ordinary tasks. The scores range from 0 to 100. A higher score means the patient is better able to carry out daily activities. KPS may be used to determine a patient's prognosis, to measure changes in a patient's ability to function. (See Appendix D)

KPS will be assessed at screening and months 1, 3, 6, 12, 18, and 24.

8.5. Quality of Life

To measure quality of life, this study will use the Short Form (SF)-12 generic measure.

SF-12 will be completed by the patient at screening, month 1 and month 3. (See Appendix F) In the event the month 1 or month 3 visit is missed, the SF-12 should be completed at the first two follow-up visits, regardless of the visit interval.

Short Form – 12 (SF-12)

The SF-12 is a shortened version of the well-known SF-36. The SF-12 assesses eight domains (physical functioning, role limitations due to physical health problems, bodily pain, social functioning, and general mental health, role limitations due to emotional problems, vitality and general health perception).

8.6. Imaging

The tumor(s) intended for ablation is referred to as the **index tumor(s)**. Index tumor evaluation will be conducted with the use of CT or FDG-PET-CT. The same method of assessment and the same technique should ideally be used to characterize each identified and reported index tumor at baseline and during follow-up. Imaging shall be performed with a minimum slice thickness of 5 mm and high resolution imaging is preferred with slice thickness of 3 mm or less. Three axes of measurements (longest diameter and the 2 perpendicular diameters) shall be evaluated and the longest dimension shall be used to determine the inclusion criteria. The use of contrast is preferred.

The cryoablation procedure will be completed under CT guidance. Week 1 follow-up imaging will be either chest CT or chest X-Ray. At months 1, 3, 6, 12, 18, and 24, follow up imaging will be chest CT or chest FDG-PET-CT.

The total area treated with cryoablation will be referred to as the **ablation zone(s)** in follow up imaging studies.

8.7. Response Determination

The month 1 post-ablation CT examination will be used as the reference for determining index ablation zone response at each follow up interval after cryoablation. Sequential follow up intervals will be used to determine local failure.

In the unforeseen circumstance where the patient is unable to complete imaging according to the month 1 follow up visit, the month 3 imaging study may serve as the reference for determining index tumor response at each follow up interval after cryoablation. Every effort should be made to comply with the month 1 imaging requirement.

Efficacy at 12 months post cryoablation will be based on local tumor control that will be separately assessed for each index tumor according to criteria below. Each ablation zone will be evaluated at each time point by measuring its 3 axes (longest diameter and the two perpendicular diameters). For each ablation zone individually, the sum of these three measures will be compared to the 1 month baseline for tumor response and the previous follow up interval imaging study for local failure.

Each ablation zone measurement assessment, along with the overall clinical evaluation of the patient, will be evaluated by an independent imaging panel to assess the final response determinations. This final review can be used in the analysis in the event of 'indeterminate' imaging measurement assessments.

Local Tumor Control will be defined as the absence of local failure.

8.7.1 Complete Response

Tumor/ablation zone disappearance or $\geq 75\%$ decrease in the 1 month baseline sum of the three axes of measurements (longest diameter and the two perpendicular diameters).

Note: If it is the opinion of the investigator that the tumor/ablation zone has likely disappeared, the measurement should be recorded as 0mm. If the tumor/ablation zone is believed to be present and is faintly seen but too small to measure, a default value of 1 mm will be assigned.

8.7.2 Partial Response

Partial response will be defined as $\geq 30\%$ decrease in the 1 month baseline sum of the three axes of measurements (longest diameter and the two perpendicular diameters).

8.7.3 Stable Disease

Stable disease will be defined as $< 30\%$ decrease in the 1 month baseline sum of the three axes of measurements (longest diameter and the two perpendicular diameters), and $< 20\%$ increase of the nadir of the 3 axes of measurements.

8.7.4 Local Failure

Local failure will be defined as $\geq 20\%$ increase in the sum of the three axes of measurements (longest diameter plus the two perpendicular diameters) when compared with the nadir of this 3 axes measurement.

9. MANUFACTURING, HANDLING AND ACCOUNTABILITY OF STUDY DEVICE AND SUPPLIES

9.1. Manufacturing, Packaging and Labeling

The Galil Medical Cryoablation System and needles are manufactured, packaged and labeled according to current Good Manufacturing Practices (cGMP) and applicable international, national and local regulations, laws, and guidelines.

9.2. Handling and Storage

The Galil Medical Cryoablation System, needles, necessary equipment, and disposables are handled and stored according to Galil Medical's specifications.

9.3. Study Supplies

Study sites will use commercially available device supplies labeled for use specifically for this study. All study supplied devices will be tracked by the sponsor and study site for accountability. A Regulatory Documents binder will be provided to each site. Questionnaires, patient instructions or applicable worksheets will also be provided to each site. The study monitor should be contacted for any issues related to these study supplies.

Cryoablation needles are supplied in individual single use, sterilized packages. Once opened, they should be used immediately for the current procedure or discarded. Cryoablation needles should be stored according to the recommendations on the commercial packaging.

9.4. Recall of Investigational Device

The Galil Medical Cryoablation System and needles are designed and built in accordance to applicable international standards for surgical medical instruments. Any recall of the study device will be done in accordance with applicable international, national and local legislation and guidelines, as well as the sponsor's requirements.

10. STATISTICAL ANALYSIS

This is a prospective, single-arm, phase II study designed to determine the safety and efficacy of Galil Medical's Cryoablation System and needles in cryoablation of metastatic lung tumors.

10.1. Study Design and Sample Size Calculation

This is a prospective, single-arm study designed to determine the safety and efficacy of Galil Medical's Cryoablation System and needles in cryoablation of metastatic lung tumors.

The primary efficacy endpoint for the trial is 12-month local tumor control. The papers shown below were used as reference for clinicians who determined a clinically relevant efficacy endpoint performance goal was 84% success at 12-months.³⁶⁻⁴³ This observed cryoablation rate will be tested against this performance goal.

Paper	Tumors	12-month Local Tumor Control Success	Lower 97.5% 1-sided Wilson CI
Okuneiff (2006)	125	91%	0.8469
Rusthoven (2009)	63	100%	0.9425
Baschnagel (2013)	47	97%	0.8757
Ricardi (2012)	77	94%	0.8632
Norihisa (2008)	43	94.50%	0.8337
Yoon (2006)	101	90%	0.8261

This test is accomplished by testing against the following hypotheses:

$$H_0: C_{\text{DEVICE}} \leq 84.0\%$$

$$H_a: C_{\text{DEVICE}} > 84.0\%$$

The null hypothesis will be rejected and the primary efficacy endpoint performance goal will be met if the lower bound of the exact one-sided 97.5% confidence interval for the six-month closure rate is greater than 84.0%.

PASS 12 was used to calculate the sample size needed. A sample size of 203 tumors achieves 85% power (and guarantees at least 80% power) to detect a difference ($P_1 - P_0$) of 0.0700 using a one-sided binomial test. The target significance level is 0.0250. The actual significance level achieved by this test is 0.0239. These results assume that the population proportion under the null hypothesis is 0.8400.

Power Analysis of One Proportion

Numeric Results for testing $H_0: P = P_0$ versus $H_1: P > P_0$

Test Statistic: Exact Test

Power	N	Proportion Given H_0 (P_0)	Proportion Given H_1 (P_1)	Target Alpha	Actual Alpha	Reject H_0 Beta If $R \geq$ This
0.8501	203	0.8400	0.9100	0.0250	0.0239	0.1499 181

To account for up-to a 10% 12-month tumor attrition rate, the final sample size has been increased to 226 tumors.

10.2. Missing Data

Missing data will be prospectively minimized through training of the participating investigator and site staff, and through appropriate clinical trial management. Every effort will be made to collect all data points in the study. All patient data that is available on patients who drop out during the course of the study will be included where possible. Sensitivity analyses will be conducted to determine the effect of missing data on the primary efficacy endpoint.

10.3. Analysis Populations

All primary efficacy analyses will be performed on all treated tumors with a Galil Medical Cryoablation System and needles as intent-to-treat population. A supplemental per-protocol analysis will be done for the primary efficacy endpoint, removing index tumor which did not have a complete treatment and/or those that did not meet the study criteria but were enrolled.

The intent-to-treat and per-protocol analyses will be compared for level of agreement. It is expected that the two tumor populations will be similar; however, any substantial differences between the two will be analyzed appropriately to elucidate the cause of these differences.

10.4. Poolability

Poolability of results across sites will also be addressed to determine if differences exist among the primary efficacy and safety endpoints and to determine if potential predictive covariates differ. For this poolability analysis, low enrolling centers may be combined into virtual center(s). Tests for comparability in terms of the primary efficacy endpoint and in terms of variables such as gender, medical history, and risk factors will be assessed.

10.5. Analysis

10.5.1. Software

Version 9.2 or higher of the SAS® statistical software package or other widely accepted statistical software will be used to provide all statistical analyses.

10.5.2. General Analysis

Data will be analyzed using descriptive statistics. Continuous variables (e.g., age) will be summarized by the number of patients, mean, standard deviation, median, interquartile range, minimum and maximum. Categorical variables (e.g., race) will be summarized by frequencies and percentages of patients in each category. 95% confidence intervals will be calculated as appropriate.

10.5.3. Primary Endpoint

The primary endpoint for this study is defined as follows: efficacy of cryoablation on local tumor control for each index tumor in patients with pulmonary metastatic disease at 12 months post cryoablation.

Patients are allowed up to 6 tumors and the primary efficacy endpoint (tumor control) will be calculated on a per tumor level. To be considered a success each tumor treated during the baseline procedure must meet the tumor control criteria at the 12 month follow-up visit.

The local tumor control counts and rates will be presented along with the 95% two-sided confidence intervals for the rates. The rate numerator will be defined as the number of tumors experiencing tumor control at 12-months. The rate denominator will be defined as the total number of tumors evaluated at 12-months.

10.5.4. Safety Data

The safety data for this study will be assessed using the incidence and severity of intra-operative events, post-operative adverse events, serious adverse events and unanticipated adverse device effects related to the cryoablation procedure.

No formal hypothesis test is being made on the safety endpoints. Point estimates and two-sided 95% confidence intervals will be generated for cryoablation related adverse events.

10.5.5. Other Data Assessments

Technically successful treatment definition

A technically successful treatment will be defined by the presence of an ablation zone, ground glass opacity, or frank consolidation encompassing the targeted index tumor(s) no later than the 1 month follow up visit after the cryoablation procedure. Technical success will be analyzed on a per tumor basis.

Disease recurrence or progression definitions

The reference date for disease progression evaluation will be associated with the initial (first) cryoablation procedure done per study protocol. In the event of multiple cryoablation procedure dates, such as with bilateral lesions or staged treatments, the date of reference for disease progression evaluation will be the initial (first of n) cryoablation procedure.

- **Local disease progression** will be determined locally by evidence of local tumor failure.
- **Lung-disease-specific survival rate** is defined as the time in days from the first cryoablation procedure to death and **a)** the date of metastatic lung tumor progression (new lung tumors or local tumor failure of the index tumor), **b)** the date of death with local control of the index tumor, or **c)** the date of last follow up in patients who were still alive with local tumor control of the index tumor. Patients who are alive will be censored at the date of their last visit. Patients who have died from causes other than local failure of the index tumor will be censored at the time of death. Lung disease-specific survival rates will be summarized by using Kaplan-Meier methodology.
- **Overall survival rate** is defined as the time in days from the first cryoablation procedure to death. Patients 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 metastatic lung disease progression beyond the index tumor** is defined as the time in days from the first cryoablation procedure to metastatic disease beyond the index tumor site. Patients without metastatic lung disease progression will be censored at the date of their last visit or their date of death (due to any cause). Metastatic progression free survival rates will be summarized by using Kaplan-Meier methodology.
- **Time to overall cancer progression** is defined as the time in days from the first cryoablation procedure to cancer progression (i.e., any location of active cancer disease). Patients without cancer progression will be censored at the date of their last visit or their date of death (due to any cause). Overall cancer progression free survival rates will be summarized by using Kaplan-Meier methodology.
- **Time to untreatable metastatic lung disease control with cryoablation** is defined as the time in days from the first cryoablation procedure to the time when the metastatic lung disease cannot be treated with cryoablation. Overall time to untreatable metastatic lung disease progression rates will be summarized by using Kaplan-Meier methodology.
- **Time to untreatable metastatic lung disease control with focal therapy** is defined as the time in days from the first cryoablation procedure to the time when the metastatic lung disease cannot be treated by focal (e.g., ablation, surgery, SBRT) intervention for control of metastatic lung disease. Overall time to untreatable metastatic lung disease progression rates will be summarized by using Kaplan-Meier methodology.

Intra-procedural data

Initial cryoablation procedure information including the tumor size and number, cryoablation needle type and the number of each type of needle used, freeze and thaw times, procedure times, and anesthesia type.

Physical performance and quality of life

Physical performance (KPS) and quality of life (SF-12) assessments will be made by examining the change in the baseline scores to those reported post-operatively as defined in Sections 8.4 and 8.5, respectively.

Subset Analyses

Analysis may be done on outcomes for subgroups including, but not limited to, gender, primary cancer and tumor size.

10.5.6. Interim Reporting

Interim reports may be prepared during the course of the study until the final study outcomes are available. The usual components of this report are:

- patient accrual rate;
- distribution of pretreatment characteristics;
- cryoablation procedure details;
- frequency and severity of the toxicities.

11. DATA MANAGEMENT

11.1. Data Collection

Patient specific data will be collected by the study coordinator. No patient specific data will be released. Deidentified data will be collected using a web-based electronic data capture (EDC) system. The system will be fully validated and compliant with FDA 21 CFR 11 guidance.

Participating sites will enter all patient data collected during the conduct of the protocol into the EDC system using the electronic case report forms (eCRFs) developed for each stage of the study. 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 patient.

All sites will receive training on the proper use of the system and the data collection expectations for this protocol. A Galil Medical representative will train each site on how to create a new patient, enter data into the eCRFs, edit/update data on existing eCRFs, resolve queries and approve/sign-off on each form/completed eCRF.

11.2. Data Processing

To help minimize data entry errors, the EDC system will include real-time edit checks that will identify potential data issues at the time of entry. These edit checks will display on-screen messages when triggered so that the investigator or data entry designee can immediately review the potential data issue and address it before leaving the form.

All eCRFs will be reviewed by clinical staff within Galil Medical to check for completeness and potential unresolved data entry issues. A Galil Medical representative 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 patient's eCRFs via electronic signature within the EDC system. The database will be subject to periodic interim analyses based on

key study milestones. Prior to each milestone analysis, a Galil Medical representative will work with each site to ensure a data set that is as complete and accurate as possible. At the conclusion of the study, 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 Galil Medical management team members.

The Institution will be provided a final electronic record of completed, locked Case Report Forms and other written records, accounts, notes and reports relating to the Study. These records will be retained for the period of time required by Applicable Laws.

12. MONITORING PROCEDURES

12.1. Monitoring and Auditing

Participating sites will be managed remotely via regular telephone contact and routine monitoring visits will be conducted. When necessary, site visits will be performed by an authorized representative from Galil Medical, and will be conducted according to the monitoring plan and applicable FDA and GCP guidelines.

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

By signing the Study Agreement, the investigator grants permission to authorized representatives of Galil Medical to conduct on-site monitoring visits for the purpose of reviewing the collected study data and to review site procedures employed in the conduct of this study.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

13. SAFETY ASSESSMENTS

All 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 AEs, SAEs and UADEs identified within the first 30 days after the cryoablation procedure will be followed and reported until resolution.

13.1. List of Definitions

Adverse Event (AE)

Any untoward or unfavorable medical occurrence in a human patient, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the patient's participation in the research, whether or not considered related to the patient's participation in the research. 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 investigator's assessment of the relationship between the AE and the study procedures.

The anticipated cryoablation related adverse events and their corresponding Common Terminology Criteria for Adverse Events (CTCAE) Terms are listed in Appendix B.⁴³

Serious Adverse Event (SAE)

Category 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 patient 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 (e.g., 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 or 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 patient 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 Effect (UADE)

Unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

13.2. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the procedure and/or study device caused or contributed to an adverse event. If the investigator's final determination of causality is unknown and the investigator does not

know whether or not the procedure and/or study device caused the event, then the event will be handled as “related to procedure or study device” for reporting purposes. If the investigator’s causality assessment is “unknown but not related to procedure or study device,” this should be clearly documented on study records.

The investigator will evaluate AEs/SAEs/UADEs 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 4.03 grading criteria
- Onset date
- Stop date
- Seriousness
 - The investigator 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 investigator must inform the Sponsor within 24 hours of knowledge of the event and complete the SAE report form.
- Relationship to Study Procedure and/or Study Device
 - The investigator must make a causality assessment for all AEs and decide whether there is a reasonable possibility the AE was caused by the procedure and/or study device.
 - If there is a valid reason to suspect a causal relationship between the AE and the procedure and/or study device, the AE should be considered “related or possibly related” to the procedure or study device.
- Outcome
- Action Taken

13.3. Recording and Reporting SAEs and UADEs

Any SAE must be reported by the investigator by calling the Galil Medical SAE reporting line (listed below) 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 [REDACTED]

Additionally, an email may be sent to [REDACTED] to report a SAE or UADE.

The investigator or designee must forward the requested follow-up information to the Galil Medical clinical representative as the event continues and/or resolves.

Investigators are required to submit to the IRB and Galil Medical a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator learns of the effect. The site must maintain adequate documentation of timely event reporting. Delegated study personnel are to enter the UADE information into the EDC system. This will prompt an automatic email confirmation of the UADE data entry to Galil Medical personnel.

It is the responsibility of the investigator to inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of SAEs/UADEs as required by local procedure. Galil Medical is responsible for relaying adequate information on SAEs/UADEs to all investigators participating in this study as well as to the FDA and other regulatory authorities.

13.4. Grading of Toxicity

Grading of toxicity will be done according to Common Terminology Criteria for Adverse Events (CTCAE, version 4.03). See anticipated adverse events in Appendix B.

14. 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



Europe



Israel



15. INVESTIGATOR REQUIREMENT

15.1. Study Initiation

Prior to enrolling patients in this study, the investigator must provide the following documents to Galil Medical:

- Signed and dated Study Agreement;
- Signed and dated Protocol Signature page;
- Signed and dated Financial Disclosure (s);
- Signed and dated Site Initiation Statement;
- A copy of the written IRB/IEC approval of the protocol;
- IRB/IEC membership roster or assurance letter;
- 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 a Galil Medical Clinical Representative 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 the study procedures and a practice session with the EDC system (when applicable). All training must be documented appropriately.

15.2. Informed Consent Form

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 Medical prior to submission to an Institutional Review Board / Independent Ethics Committee (IRB/IEC). A copy of the IRB/IEC-approved document along with the supporting IRB/IEC documentation must be submitted to Galil Medical prior to its use.

An approved ICF, including HIPAA language, must be signed by each patient, or the patient's legally authorized representative, before he is subject to any study 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 patient, or the patient's legally authorized representative. The original signed ICF is to be kept with the patient's study 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 study. This overview will include a discussion of the study's purpose and objectives, the scope and duration of participation and the disclosure that the patient may withdraw from the study 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.

15.3. Institutional Review Board/Independent Ethics Committee

This protocol, the Informed Consent Form (ICF) and relevant supporting information must be submitted to an IRB/IEC before a site is initiated for participation. Approval from the IRB/IEC must be obtained before any study assessments are performed. IRB/IEC approval shall be documented in a letter to the investigator, clearly identifying this protocol, the documents reviewed and the date of approval. This protocol 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 study and of any protocol changes, as necessary. Galil Medical will be responsible for updating the study's central IRB/IEC, if applicable.

Investigators are required to notify their local IRB/IEC of all Serious Adverse Events (SAEs) and all Unexpected Adverse Device Events (UADEs). Investigators under the jurisdiction of the study's central IRB/IEC are required to promptly notify Galil Medical of such events so that Galil Medical can notify the central IRB/IEC.

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

15.4. Protocol Amendments

This protocol will only be altered by written amendments. Administrative changes that do not impact patient participation in the study or that have the potential to affect data integrity 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.

15.5. Record Retention

All source documents, records and reports related to data provided to this study will be retained by the investigator in accordance with applicable FDA regulations, ICH and GCP guidelines for at least two (2) years following closure of the study. 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 Medical.

16. STUDY COMMITTEE

16.1. Medical Monitor

An independent Medical Monitor will be designated to ensure the safety of patients throughout the duration of the study through regular review and analysis of the safety data. In the event the Medical Monitor and the Investigator disagree on adverse event analysis, an independent adjudicator will be retained for review and resolution.

16.2. Central Imaging Review

Index tumor imaging following cryoablation will be assessed by individual study site investigators. Deidentified images will be assessed by a qualified third party central reviewer for assessment and

adjudication. The image review will be conducted by physicians who are board certified in radiology with experience in tumor assessment following ablation.

17. STUDY ADMINISTRATION

Galil Medical will make necessary efforts to ensure that this study is conducted in compliance with all applicable regulatory requirements.

17.1. Study Registration

Information about this study will be registered and updated on www.clinicaltrials.gov.

17.2. Study Discontinuation

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

- Unsatisfactory enrollment;
- Inability to ensure consistent follow-up data collection;
- Other ethical or clinical considerations.

17.3. Discontinuation of a Study Site

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

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

18. CONFIDENTIALITY/PUBLICATION OF STUDY RESULTS

This clinical study is confidential and should not be discussed with individuals outside the study. Additionally, the information in this document and in the study may contain secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by federal or state law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the study that have a need to know, but all such persons must be instructed not to further disseminate this information to others.

The data may be used now and in the future for presentation or publication at the sponsor's discretion or for submission to governmental regulatory agencies.

All reports and communications relating to patients in the study will identify each patient only by the patient's initials and by the patient's study number.

Final study data will be posted to www.clinicaltrials.gov according to the regulatory posting requirements.

19. STUDY COMPLETION

The investigator will complete and report the study in satisfactory compliance with the protocol. It is agreed that, for any reasonable cause, either the investigator or the sponsor, Galil Medical, may terminate this study, provided a written notice is submitted at a reasonable time in advance of intended termination. If the study is terminated for safety reasons, the investigator will be notified immediately by telephone, followed by written instructions for study termination notification of the IRB.

20. PROTOCOL DEVIATIONS AND EXCEPTIONS

The investigator should not implement any deviation from or changes to the protocol without agreement by the sponsor and prior review and documented approval from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

The investigator should document and explain any deviation from the approved protocol. The reasons for it and, if appropriate, the proposed protocol amendments should be submitted to the Sponsor for agreement, the IRB/IEC and to the regulatory authority (when applicable).

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22. APPENDIX A: ABBREVIATIONS

Acronym	Definition
AE	Adverse Event
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FDG-PET-CT	Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography
G	Gauge (e.g. 17G)
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB/IEC	Institutional Review Board/Independent Ethics Committee
INR	International normalized ratio
KPS	Karnofsky Performance Scale
SAE	Serious Adverse Event
SF-12	Short Form – 12
UADE	Unanticipated Adverse Device Effect

23. APPENDIX B: ANTICIPATED ADVERSE EVENTS AND CTCAE TERMS

ADVERSE EVENT	CTCAE TERM (4.03)
Allergic Reaction/hypersensitivity	Allergic reaction
Angina	Acute coronary syndrome
Atelectasis	Atelectasis
Atrial fibrillation	Atrial fibrillation
Atrial flutter	Atrial flutter
Bronchial fistula	Bronchial fistula
Bronchial infection	Bronchial infection
Bronchopleural fistula	Bronchopleural fistula
Bronchopulmonary hemorrhage	Bronchopulmonary hemorrhage
Cardiac arrest	Cardiac arrest
Cardiac disorders - Other, Specify	
Cardiac troponin T increased	Cardiac troponin T increased
Chest wall pain	Chest wall pain
Cough	Cough
Death NOS	Death NOS
Dyspnea	Dyspnea
Ecchymosis/bruising	Bruising
Electrocardiogram QT corrected interval prolonged	Electrocardiogram QT corrected interval prolonged
Hematoma	Hematoma
Hemoptysis	Bronchopulmonary hemorrhage
Hypothermia	Hypothermia
Infections and infestations - Other, specify	
Injection site reaction	Injection site reaction
Intraoperative arterial injury	Intraoperative arterial injury
Intraoperative hemorrhage	Intraoperative hemorrhage
Intraoperative respiratory injury	Intraoperative respiratory injury
Intraoperative venous injury	Intraoperative venous injury
Lung infection	Lung infection
Mediastinal hemorrhage	Mediastinal hemorrhage
Mediastinal infection	Mediastinal infection

ADVERSE EVENT	CTCAE TERM (4.03)
Mucosal infection	Mucosal infection
Myocardial infarction	Myocardial infarction
Nausea	Nausea
Neuropathy: Sensory (e.g., lumbar radiculopathy)	Peripheral sensory neuropathy
Non-cardiac chest pain	Non-cardiac chest pain
Pain at needle site	Refer to Pain
Pain, not at needle site	Refer to Pain at location "x"
Paroxysmal atrial tachycardia	Paroxysmal atrial tachycardia
Pericardial tamponade	Pericardial tamponade
Peripheral motor neuropathy	Peripheral motor neuropathy
Pleural effusion	Pleural effusion
Pleural hemorrhage	Pleural hemorrhage
Pleural infection	Pleural infection
Pleuritic pain	Pleuritic pain
Pneumonitis	Pneumonitis
Pneumothorax	Pneumothorax
Postoperative hemorrhage	Postoperative hemorrhage
Postoperative thoracic procedure complication	Postoperative thoracic procedure complication
Probe site paresthesia (tingling, numbness)	Paresthesia
Pulmonary edema	Pulmonary edema
Pulmonary Failure/ARDS	Adult respiratory distress Syndrome
Pulmonary failure/hypoxia	Hypoxia
Pulmonary fistula	Pulmonary fistula
Pulmonary hypertension	Pulmonary hypertension
Respiratory failure	Respiratory failure
Respiratory, thoracic and mediastinal disorders - Other, specify	
Seroma	Seroma
Sinus bradycardia	Sinus bradycardia
Sinus tachycardia	Sinus tachycardia
Skin burn/frostbite	Burn
Skin infection	Skin infection
Soft tissue infection	Soft tissue infection

ADVERSE EVENT	CTCAE TERM (4.03)
Stroke	Stroke
Sudden death NOS	Sudden death NOS
Supraventricular tachycardia	Supraventricular tachycardia
Surgical and medical procedures - Other, specify	
Thromboembolic event	Thromboembolic event
Thrombosis/embolism (vascular access)	Vascular access complication
Tracheal fistula	Tracheal fistula
Transient ischemic attack	Transient ischemic attack
Tumor pain	Tumor pain
Upper respiratory infection	Upper respiratory infection
Vagal reaction	Vasovagal reaction
Ventricular arrhythmia	Ventricular arrhythmia
Ventricular fibrillation	Ventricular fibrillation
Ventricular tachycardia	Ventricular tachycardia
Vomiting	Vomiting
Wound complication (e.g., hernia)	Wound complication
Wound dehiscence	Wound dehiscence
Wound infection (e.g., abscess)	Wound infection

24. APPENDIX C: KARNOFSKY PERFORMANCE STATUS (KPS)

The Karnofsky Performance Scale allows patients to be classified as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients.

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

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25. APPENDIX D: ASA Physical Status Classification System

ASA Physical Status 1	A normal healthy patient
ASA Physical Status 2	A patient with mild systemic disease
ASA Physical Status 3	A patient with severe systemic disease
ASA Physical Status 4	A patient with severe systemic disease that is a constant threat to life
ASA Physical Status 5	A moribund patient who is not expected to survive without the operation
ASA Physical Status 6	A declared brain dead patient whose organs are being removed for donor purposes

26. APPENDIX E: QUALITY OF LIFE (SF-12)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
Required parameters are missing or incorrect.	Required parameters are missing or incorrect.	Required parameters are missing or incorrect.	Required parameters are missing or incorrect.	Required parameters are missing or incorrect.
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Yes, limited a lot	Yes, limited a little	No, not limited at all
Required parameters are missing or incorrect.	Required parameters are missing or incorrect.	Required parameters are missing or incorrect.

- Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf..... 1 2 3
- Climbing several flights of stairs 1 2 3

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
Required parameters are missing or incorrect	Required parameters are missing or incorrect	Required parameters are missing or incorrect	Required parameters are missing or incorrect	Required parameters are missing or incorrect

- Accomplished less than you would like 1 2 3 4 5
- Were limited in the kind of work or other activities 1 2 3 4 5

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
Required parameters are missing or incorrect	Required parameters are missing or incorrect	Required parameters are missing or incorrect	Required parameters are missing or incorrect	Required parameters are missing or incorrect

• Accomplished less than you would like ₁ ₂ ₃ ₄ ₅

• Did work or other activities less carefully than usual ₁ ₂ ₃ ₄ ₅

4. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
Required parameters are missing or incorrect.	Required parameters are missing or incorrect.	Required parameters are missing or incorrect.	Required parameters are missing or incorrect.	Required parameters are missing or incorrect.
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

5. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

All of the time	Most of the time	Some of the time	A little of the time	None of the time
Required parameters are missing or incorrect.	Required parameters are missing or incorrect.	Required parameters are missing or incorrect.	Required parameters are missing or incorrect.	Required parameters are missing or incorrect.

• Have you felt calm and peaceful? ₁ ₂ ₃ ₄ ₅

• Did you have a lot of energy? ₁ ₂ ₃ ₄ ₅

• Have you felt downhearted and depressed? ₁ ₂ ₃ ₄ ₅

6. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
Required parameters are missing or incorrect.	Required parameters are missing or incorrect.	Required parameters are missing or incorrect.	Required parameters are missing or incorrect.	Required parameters are missing or incorrect.
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

Thank you for completing these questions!