



Protocol Signature Page


PROTOCOL TITLE: Evaluating Cryoablation of Metastatic Lung/Pleura Tumors in Patients – Safety and Efficacy (ECLIPSE)
PROTOCOL NUMBER: CUC10-LNG06-04
PHASE: 1
DATE: 09 AUG 2011

Galil Protocol Approval

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


Director, Clinical Research


Signature


Director, Regulatory Affairs

Investigatory 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

PROTOCOL TITLE: Evaluating Cryoablation of Metastatic Lung/Pleura Tumors in Patients – Safety and Efficacy (ECLIPSE)

PROTOCOL NUMBER: CUC10-LNG06-04

PHASE: 1

SPONSOR: Galil Medical
4364 Round Lake Rd.
Arden Hills, MN 55112

PROTOCOL [REDACTED]
RESPONSIBILITY: Director Clinical Research

DATE: 09 AUG 2011

This document contains confidential information belonging to Galil Medical. Except as otherwise agreed to in writing, by accepting or reviewing this document, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Galil Medical must be promptly notified.

Do not copy or distribute without written permission.

Table of contents

1.	INTRODUCTION	5
1.1.	History of Cryotherapy	5
1.1.	Historical Background of Metastatic Lung Cancer	6
1.2.	Metastatic Lung Cancer Treatment Options	6
2.	DEVICE DESCRIPTION	7
3.	CLINICAL BACKGROUND	7
3.1.	Cryoablation in the Treatment of Lung Tumors	7
3.2.	Previous Clinical Studies Leading Up to and Supporting the Proposed Research	7
3.3.	Rationale Behind the Proposed Research	9
4.	STUDY OBJECTIVE	9
4.1.	Study Objective	9
5.	STUDY DESIGN	9
5.1.	Efficacy Endpoints	9
5.2.	Safety Endpoints	9
5.3.	Other Endpoints	9
5.4.	Tumor Characteristics	9
5.5.	Physical Function	10
5.6.	Quality of Life	10
6.	STUDY TREATMENTS	10
6.1.	Treatment	10
6.2.	Additional Treatment	10
6.3.	Patient Enrollment	10
6.4.	Patient Withdrawal	11
6.5.	Risks	11
6.6.	Potential Benefits	11
6.7.	Study Supplies	11
6.8.	Pertinent Concurrent Medications	11
7.	PATIENT POPULATION	12
7.1.	Patient Selection	12
7.2.	Inclusion Criteria	12
7.3.	Exclusion Criteria	12
8.	STUDY PROCEDURES	13
8.1.	Screening	13
8.2.	Cryoablation Procedure	14
8.3.	Week 1 – Follow-up	15
8.4.	Month 1 – Follow-up (Telephone Interview or Clinic Visit)	16

8.5.	Months 3, 6 and 12 – Follow-up	16
8.6.	Months 24, 36, 48, 60 and Study Completion or Withdrawal	16
9.	ASSESSMENTS	17
9.1.	Demography	17
9.2.	Targeted Medical History	17
9.3.	Laboratory Tests	17
9.3.1.	Biopsy	17
9.4.	Physical Performance	17
9.5.	Quality of Life	17
9.6.	Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)	18
9.7.	Response Determination	18
10.	ENGINEERING, MANUFACTURING, HANDLING AND ACCOUNTABILITY OF INVESTIGATIONAL DEVICE	18
10.1.	Manufacturing, Packaging and Labeling	18
10.2.	Handling and Storage	18
10.3.	Recall of Investigational Device	19
11.	STATISTICAL ANALYSIS	19
11.1.	General Methods	19
11.2.	Sample Size	19
11.3.	Missing Data	19
11.4.	Analysis Populations	19
11.5.	Analysis	19
12.	DATA MANAGEMENT	21
12.1.	Data Collection	21
12.2.	Data Processing	21
13.	MONITORING PROCEDURES	21
13.1.	Monitoring and Auditing	21
14.	SAFETY ASSESSMENTS	22
14.1.	List of Definitions	22
14.2.	Causality Assessment	23
14.3.	Recording and Reporting SAEs and UADEs	23
15.	PRODUCT COMPLAINTS	24
16.	INVESTIGATOR REQUIREMENT	24
16.1.	Study Initiation	24
16.2.	Informed Consent Form	25
16.3.	Institutional Review Board/Independent Ethics Committee	25
16.4.	Protocol Amendments	25
16.5.	Record Retention	25

17.	STUDY COMMITTEE _____	26
17.1.	Medical Monitor _____	26
18.	STUDY ADMINISTRATION _____	26
18.1.	Study Registration _____	26
18.2.	Study Discontinuation _____	26
18.3.	Discontinuation of a Study Site _____	26
19.	CONFIDENTIALITY/PUBLICATION OF STUDY RESULTS _____	26
20.	STUDY COMPLETION _____	27
21.	PROTOCOL DEVIATIONS AND EXCEPTIONS _____	27
22.	REFERENCES _____	28
23.	APPENDIX A: ABBREVIATIONS _____	30
24.	APPENDIX B: ANTICIPATED ADVERSE EVENTS AND CTCAE TERMS _____	31
25.	APPENDIX C: PERFORMANCE STATUS SCORING (ECOG) _____	34
26.	APPENDIX D: KARNOFSKY PERFORMANCE STATUS (KPS) _____	35
27.	APPENDIX E: QUALITY OF LIFE (SF-12) _____	36

TABLE of TABLES

Table 1: Schedule of Study Events.....	13
--	----

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

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 gasses,^{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.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, Ltd. (Yokneam, Israel) 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 cryoablation needle forms a different shape and size of iceball. Multiple cryoablation needles may be inserted into the tumor, or even into 2 or 3 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.

Tissue thermal sensors may be employed to enable the real-time tissue temperature monitoring, thus, contributing to the safety and effectiveness of the procedure.

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

1.1. Historical Background of Metastatic Lung Cancer

The first surgical resection of a pulmonary metastasis (sarcoma) dates back to 1882 and is credited to Weinlechner. Barney and Churchill performed the first isolated resection of a pulmonary metastasis in the United States in 1939. In the past 25 years, surgical resection has become widely accepted for the treatment of pulmonary metastases.²¹

Today, lung cancer is the most frequent malignancy causing death in the world. Common primary tumors that usually present as lung metastasis are breast, colon, kidney, uterus and cervix, prostate, and head and neck tumors. Though surgery, with or without systemic chemotherapy, remains the treatment option of choice, not all patients are considered appropriate candidates for this treatment option.²² Therefore, it is necessary to develop alternative, less invasive treatments for patients who are not candidates for surgery.

1.2. Metastatic Lung Cancer Treatment Options

The choice of treatment depends mainly on the type of lung cancer and its stage. Treatment may include surgery, chemotherapy, radiation therapy, targeted therapy, or a combination of treatments, depending on the stage and size of the tumor. Treatment may be local or systemic.²³

Surgery is typically the best option with localized disease (no mediastinal invasion), however only 25% of tumors are suitable at the time of diagnosis for potential curative resection. Chemotherapy and/or external beam radiation (XRT) with chemotherapy is generally the standard treatment for regional disease. If the primary malignancy is controlled and there is no evidence of extrathoracic disease, then resection may be considered.²² Besides the traditional treatment options, minimally invasive treatment options include stereotactic radiotherapy, brachytherapy, bronchial arterial infusion of chemotherapy, photodynamic therapy and thermal ablation. Ablative technologies that are emerging as treatment options for lung cancer tumors include radiofrequency, microwave and cryoablation.²²

2. DEVICE DESCRIPTION

Galil Medical's Cryoablation Systems (Galil Medical, Ltd, Yokneam, Israel) 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.

3. CLINICAL BACKGROUND

3.1. Cryoablation in the Treatment of Lung Tumors

Ablation of lung tumors is the fastest expanding area within interventional oncology. Radiofrequency, laser, microwave and cryotherapy have all been shown to be effective.²⁴ Cryotherapy has 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. Additionally, only minor discomfort at the procedure site has been noted and this typically resolves within 48 hours of the procedure. Cryoablation has been 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 basic CT guidance.²⁵

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

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 cryosurgery 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 cryosurgery 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 cryosurgery 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.²⁶

Kawamura et al reported a series of 35 tumors in 20 patients treated with cryosurgery 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 cryosurgery sessions. Pneumothorax occurred in 11 of 22 treatment sessions. Seven cases of pleural effusion, 8 cases of hemoptysis, and 1 case of phrenic nerve palsy were reported. 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. 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 patients developed a local recurrence of 7 (20%) of tumors in 7 (35%) patients. Five patients underwent additional cryosurgery without complication or local recurrence. Pneumothorax was reported in 50% of the cases, 27% experienced pleural effusion, 41% hemoptysis, and 4.5% phrenic nerve palsy. The Kaplan Meier 1-year survival was 89.4%.²⁷

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. PCT 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 cryosurgery. 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. Larger areas of cavitation were noted at the 1 week interval, however areas nearly resolved by 3 months with only 7% of masses still showing cavitation. Cavitation was noted to be a good indicator of thorough tumor ablation coverage and 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.²⁸

3.3. Rationale Behind the Proposed Research

Less than 25% of patients diagnosed with lung cancer have localized disease and are surgical candidates. There are many different methods of for treating pulmonary metastatic disease. Surgery is typically used when the disease is localized and chemotherapy with or without XRT is used when the disease is regional. However, several variables may exclude patients from these treatments.

The target population for this study is patients with pulmonary metastatic disease 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 feasibility of cryoablation in local tumor control for tumors ≤ 3.5 cm in patients with pulmonary metastatic disease.

5. STUDY DESIGN

This is a Phase 1 multicenter, prospective, single arm study with patients serving as their own control. This study is to enroll at least 30, but up to 40, patients who 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 within 6 weeks of the cryoablation procedure. After the cryoablation procedure visit date, follow-up visits will consist of within 1 Week of the cryoablation procedure and then 1, 3, 6, 12, 24, 36, 48 and 60 months post cryoablation procedure.

5.1. Efficacy Endpoints

The efficacy endpoint for this study is defined as follows:

- Assessing the effectiveness of cryoablation on local tumor control in patients with pulmonary metastatic disease at 3, 6, 12, 24, 36, 48 and 60 months post cryoablation.

5.2. Safety Endpoints

The safety endpoint for this study is to assess the incidence and severity of cryoablation related adverse events.

5.3. Other Endpoints

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

- Assessing overall disease specific survival at 3, 6, 12, 24, 36, 48 and 60 months post cryoablation.
- Assessing time to disease recurrence or progression.
- Assessing the changes in physical function and quality of life over time. (See Section 11.5.4)
- Assessing cryoablation technical success. (See Section 11.5.4)

5.4. Tumor Characteristics

Tumor characteristics will be recorded at baseline.

5.4.1. Characteristics

Tumor characteristics will include, but are not limited to:

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

5.5. Physical Function

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

This study will use ECOG and 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 was selected because it will reduce participant burden yet still give a general measure of quality of life.

6. STUDY TREATMENTS

6.1. Treatment

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.

6.2. Additional Treatment

Patients may not receive additional local treatment to the index tumor(s) subjected to cryoablation while participating in the study protocol. If additional local treatment (e.g. ablation, surgery, radiation) is required, then the patient must be withdrawn from the study.

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

6.3. 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.

6.4. Patient 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. As 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.

6.5. Risks

Potential risks of pulmonary tumor cryoablation in the intra operative/early postoperative period include bleeding, cough, hemoptysis, fever, hypertension, pleural effusion, pneumothorax, subcutaneous emphysema and skin injury.

Potential delayed risks of pulmonary tumor cryoablation include pulmonary embolus, acute respiratory distress syndrome and other unforeseen complications.

6.6. Potential Benefits

Cryoablation is an FDA-cleared treatment modality for the ablation of cancerous or malignant tissue and benign tumors, and palliative intervention. Potential benefits of pulmonary tumor cryoablation include palliative relief of symptoms associated with the disease including dyspnea, cough and hemoptysis. Other benefits may include improved lung function and performance status.

6.7. Study Supplies

Study sites will use commercially available device supplies labeled for use specifically for this study. A Regulatory Documents binder will be provided to each site. Questionnaires, patient instructions and 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.

6.8. Pertinent Concurrent Medications

Data will be collected regarding concurrent pertinent medication taken at the time of screening and through 30 days post procedure. Patients who are taking any contraindicated medications at screening must appropriately wash out before the cryoablation procedure. 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 be washed out of 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 the patient's participation in the study may need to be discontinued due to non-permitted concurrent therapy.

7. PATIENT POPULATION

7.1. 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.

7.2. Inclusion Criteria

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

- 7.2.1. Patient must be at least 18 years old.
- 7.2.2. Patient has signed a written informed consent.
- 7.2.3. 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 or MRI) with known (biopsied) primary disease.
- 7.2.4. Patient has up to 3 local metastases unilaterally targeted by cryoablation. (treatment in both lungs must be on separate treatment days) Maximum number of pulmonary tumors bilaterally per patient will be 5 total pulmonary tumors.
- 7.2.5. Targeted tumor(s) defined as intra pulmonary or pleural with a maximum size of 3.5 cm.
- 7.2.6. The target tumor is determined (by CT/MRI images) to be in a location where cryoablation is technically achievable based on the proximity of adjacent organs and structures.
- 7.2.7. ECOG performance status of 0-2.
- 7.2.8. Karnofsky Performance Scale (KPS) score ≥ 60 .
- 7.2.9. Platelet count $>50,000/\text{mm}^3$ within 60 days prior to study treatment.
- 7.2.10. INR <1.5 within 60 days prior to study treatment.
- 7.2.11. Patient has a life expectancy of >3 months.
- 7.2.12. Patient is clinically suitable for cryoablation procedure.

7.3. Exclusion Criteria

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

- 7.3.1. Patient's primary cancer is lung cancer.
- 7.3.2. Patient is unable to lie flat or has respiratory distress at rest.
- 7.3.3. Patient has uncontrolled coagulopathy or bleeding disorders.
- 7.3.4. Patient has had chemotherapy with neutropenia to levels (ANC <1000) that produce increase risk for the cryoablation procedure.
- 7.3.5. Patient has a history of an allergic reaction to iodine injections or to shellfish.
- 7.3.6. Patient has evidence of active systemic, pulmonary, or pericardial infection.
- 7.3.7. Patient has a debilitating medical or psychiatric illness that would preclude giving informed consent or receiving optimal treatment or follow up.
- 7.3.8. Patient is currently participating in other experimental studies that could affect the primary endpoint.

8. 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 11 visits, including an initial/screening visit, the procedure visit, and 9 post-operative visits. The Month 1 post-operative visit may be a telephone visit or a clinic visit. More visits may be required when medically necessary.

Table 1: Schedule of Study Events

Procedures	Screening	Procedure Date	W 1 ^a	M 1 ^b	M 3, 6 & 12 ^d	M 24, 36, 48, 60 ^e or Withdrawal
Informed Consent	X					
Inclusion/Exclusion	X					
Demographics	X					
Targeted Medical History	X					
ECOG & Karnofsky	X		X	X ^c	X	X
Pertinent Medication	X		X	X		
Discontinue anticoagulation, as clinically indicated	X					
CT/MRI Scan ^f	X		X ^g		X	X
Record tumor characteristics	X					
Chest X-Ray			X ^g			
Cryoablation procedure		X				
Labs ^h	X					
Quality of Life (SF-12) ⁱ	X			X	X	X
Safety Assessments		X	X	X	X	X

^a Week 1 visit within +/- 7 days of cryoablation procedure

^b Month 1 visit may be done by telephone interview or clinic visit. Visit window +21/-7 days

^c Complete only if a Clinic Visit

^d Months 3, 6 and 12 visit window ± 45 days

^e Months 24, 36, 48 and 60 visit window ± 90 days

^f CT/MRI scan with contrast for follow-up at 3 months, 6 months, 1 year then yearly per routine post treatment f/u

^g Week 1 imaging may be a CT, MRI or X-Ray with or without contrast

^h Platelet Count, ANC and INR – within 60 days of study procedure

ⁱ To be completed before treatment starts then at 1, 3, 6, 12, 24, 36, 48 and 60 months post cryoablation

8.1. Screening

The screening period begins after written informed consent has been obtained. The screening visit allows the investigator to assess a patient's eligibility for this study.

The following assessments will be completed during screening and within 6 weeks of the cryoablation procedure:

- Informed consent;
- Review inclusion/exclusion criteria;
- Patient number assigned;
- Demography;
- Targeted medical history, including comorbidities;
- ECOG;
- Karnofsky Performance Scale;
- Baseline labs (Platelet Count, ANC and INR);
- CT/MRI scan of chest with contrast to include lungs, liver, and adrenal glands;
- Tumor characteristics (See Section 5.4);
- Quality of Life assessments (SF-12);
- Current pertinent concomitant medication;
- Discontinue anticoagulation as clinically indicated;
- Assess for clinical safety of General Anesthesia (if applicable).

8.2. Cryoablation Procedure

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:

- Number of tumors treated with cryoablation
- Tumor size measured by two methods:
 - 3-dimensional measurements (cm) and
 - Greatest trans-axial diameter (cm)
- 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)
- Requirement for hospital admittance/stay
- Requirement for surgical intervention(s)
- Safety assessments

8.2.1. Cryoablation needle placement

Based upon isotherm data for the cryoablation needles, the distance between adjacent cryoablation needles should be ≤ 15 mm. 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 lung tumor at the time of treatment.

The CT imaging views of the lung tumor 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 tumor and provide a 5 mm zone of ablation surrounding the tumor while maintaining appropriate safe distance from the non-targeted tissues (i.e. main bronchus and pulmonary arteries).

8.2.2. 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.

8.2.3. Freezing procedure

Once freezing has been initiated, the cryoablation procedure may be monitored with non-contrast CT imaging at 2-5 minutes intervals 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 ablation zone should be monitored continuously under CT imaging guidance during the procedure. When the leading edge of the ice has reached at least 5 mm beyond the tumor periphery, the freezing process should be stopped. Typically, three freeze-thaw cycles should be utilized. Passive or active thaw should be carried out with at least a 5 minute thaw between freeze cycles. Following the last freeze cycle, a brief (up to 10 minute) active thaw should be utilized prior to attempting to remove the needle(s). Passive thawing will complete the melting of the ice. A technically successful treatment will be defined as an ablative margin of at least 5 mm beyond the edge of the tumor.

8.2.4. Procedure completion

CT images are typically obtained in the transverse and longitudinal planes showing the greatest extent of freeze. On the transverse view, the medial extent of the ice should encompass all treated tissue at least 5 mm beyond the tumor periphery. After cryoablation needle removal, CT images will be obtained to assess any bleeding or pneumothorax development. If a pneumothorax is diagnosed it should be managed per standard of care.

If intrapulmonary, endobronchial, or intrapleural bleeding occurs, a clinical assessment will determine whether transfusion is necessary and subsequent CT imaging will determine whether the bleeding is increasing over time. If the bleeding continues to increase over time, it will be managed per standard of care.

An antibiotic of choice can be prescribed to prevent post-operative infection.

8.3. Week 1 – Follow-up

Within 1 Week (+/- 7 days) post cryoablation procedure patients are to complete the following assessment:

- ECOG;
- Karnofsky Performance Scale;
- Chest x-ray or CT/MRI, with or without contrast;

- Safety assessments;
- Surgical intervention(s), as applicable;
- Current pertinent concomitant medication.

8.4. Month 1 – Follow-up (Telephone Interview or Clinic Visit)

Patients may be contacted by telephone or return 1 Month (+21/-7 days) post cryoablation procedure to complete the following assessments:

- Quality of Life assessments (SF-12);
- ECOG (Clinic Visit Only);
- Karnofsky Performance Scale (Clinic Visit Only);
- Safety assessments;
- Assess any new cancer treatment(s);
- Current pertinent concomitant medication.

8.5. Months 3, 6 and 12 – Follow-up

Patients will return 3, 6 and 12 Months (+/-45 days) post cryoablation procedure to complete the following assessments:

- ECOG;
- Karnofsky Performance Scale;
- Quality of Life assessments (SF-12);
- CT/MRI Scan, with contrast;
- Safety assessments;
- Assessment of disease progression, including retreatment;
- Assess any new cancer treatment(s).

8.6. Months 24, 36, 48, 60 and Study Completion or Withdrawal

Patients will return 24, 36, 48 and 60 months (+/- 90 days) post cryoablation procedure or at Study Withdrawal and complete the following assessments:

- ECOG;
- Karnofsky Performance Scale;
- Quality of Life assessments (SF-12);
- CT/MRI Scan, with contrast;
- Safety assessments;
- Assessment of disease progression, including retreatment;
- Assess any new cancer treatment(s).

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

Patients may be considered “lost to follow-up” after 3 unsuccessful attempts to contact the patient with on 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.

9. ASSESSMENTS

9.1. Demography

Demographic information will be collected from the patient during screening. The information will consist of date of birth, race and sex.

9.2. 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.

9.3. Laboratory Tests

Laboratory tests will be performed by the site's local laboratory. The following laboratory tests are required within 6 weeks of the cryoablation procedure.

- Platelet Count;
- ANC;
- INR.

9.3.1. 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.

9.4. Physical Performance

Physical function assessments will be measured using Eastern Cooperative Oncology Group (ECOG) and Karnofsky Performance Scale (KPS).

Performance Status – ECOG

A set of criteria with corresponding scores used by the investigator to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. (See Appendix C)

ECOG will be assessed at screening, Week 1 and Months 3, 6, 12, 24, 36, 48 and 60.

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, Week 1 and Months 3, 6, 12, 24, 36, 48 and 60.

9.5. 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, Months 1, 3, 6, 12, 24, 36, 48 and 60. (See Appendix E)

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, general mental health, role limitations due to emotional problems, vitality and general health perception).

9.6. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

As outlined in this protocol, all patients will have an initial CT or MRI prior to therapy. The cryoablation procedure will be completed under CT guidance only. Follow-up imaging at Week 1 will be either CT, MRI or X-Ray. At Months 3, 6, 12, 24, 36, 48 and 60, follow up imaging will be CT or MRI with contrast unless contrast is contraindicated.

9.7. Response Determination

The tumor(s) treated will be defined as the target tumor. The baseline size(s) will be measured on the pretreatment CT/MRI scan.

Local tumor control will be defined as follows:

9.7.1. Local Control

Local control will be defined as the absence of local failure.

9.7.2. Complete Response

Tumor disappearance (scar) or <25% of original size.

Note: If it is the opinion of the investigator that the tumor has likely disappeared, the measurement should be recorded as 0mm. If the tumor is believed to be present and is faintly seen but too small to measure, a default value of 5mm will be assigned.

9.7.3. Partial Response

Partial response will be defined as >30% decrease in the sum of the largest diameter of all targeted tumors.

9.7.4. Stable Disease

Stable disease will be defined as <30% decrease in the sum of the largest diameter of all targeted tumors.

9.7.5. Local Failure

Local failure will be defined as >20% increase in the sum of the largest diameter of all targeted tumors.

9.7.6. Distant Failure

Distant failure (e.g. metastatic disease) will be defined as the appearance of distant cancer deposits consistent with metastatic spread of cancer outside the intended treatment area.

10. ENGINEERING, MANUFACTURING, HANDLING AND ACCOUNTABILITY OF INVESTIGATIONAL DEVICE

10.1. 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.

10.2. Handling and Storage

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

10.3. Recall of Investigational Device

The Galil Medical Cryoablation System and needles are designed and built in accordance to IEC 60601-1 standard performance and safety specifications for surgical medical instruments. Any recall of the investigational device will be done in accordance with applicable international, national and local legislation and guidelines, as well as the sponsor's requirements.

11. STATISTICAL ANALYSIS

11.1. General Methods

This is a prospective single-arm feasibility study designed to determine the safety of Galil Medical's Cryoablation System and needles in cryoablation of lung tumors, as well as give an insight into the efficacy of the treatment. This study is not powered for formal statistical analysis. All comparisons will be qualitative in nature. Descriptive results of this feasibility study may be used to generate hypotheses for a pivotal study.

11.2. Sample Size

Because estimates from this study will be used to power the pivotal study, this study must be able to provide such estimates. A sample size of at least 30 patients, but up to 40 patients, is considered clinically sufficient to give indications of both safety and potential efficacy. With this sample size, we feel we can decide whether to proceed to a pivotal study, determine endpoints for such a study, and design the study to answer the proposed hypotheses. Up to approximately 10 additional patients may be enrolled to account for patients who do not meet inclusion/exclusion criteria involving non-standard clinical practices.

11.3. 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.

11.4. Analysis Populations

All analyses will be performed on all subjects with a Galil Medical Cryoablation System and needles as the attempted treatment. A per-protocol analysis may also be done, removing subjects who did not have a complete treatment and those that did not meet the study criteria but were enrolled.

11.5. Analysis

11.5.1. 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.

11.5.2. Efficacy Endpoints

The efficacy endpoint for this study is defined as follows: local tumor control in patients with pulmonary metastatic disease at 3, 6, 12, 24, 36, 48 and 60 months post cryoablation.

Tumor control will be determined by examining the change from baseline at follow-up visits. Post-treatment imaging including CT/MRI will be reported for baseline and follow-up visits. Tumor control will be defined by the criteria defined in Section 9.7 of this protocol.

Patients are allowed up to 5 tumors so tumor control will be calculated on a per tumor level as well as a patient level. To be considered a success on a patient level all tumors treated during the baseline procedure must meet the tumor control criteria at that 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 at the each visit will be defined as the proportion of tumors/patients experiencing tumor control at a specific timepoint out of the number of patients who complete a follow-up visit at that timepoint.

11.5.3. Safety Endpoints

The safety endpoint for this study is to assess 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.

Point estimates and two-sided 95% confidence intervals will be generated for cryoablation related adverse events.

11.5.4. Other Endpoints

Technically successful treatment definition

A technically successful treatment will be defined by an ablation volume encompassing the tumor with at least a 5 mm margin.

Technical success will be calculated on a per tumor level as well as a patient level. To be considered a technical success on a patient level all tumors treated during the baseline procedure must meet the technical success criteria.

Disease recurrence or progression definitions

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

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

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

Intra-procedural data

Initial cryoablation procedure information including the type of procedure, tumor size and number, cryoablation needle type and the number of each type of needle used, freeze and thaw times, method of thaw (active or passive), and ice formation and how it encompasses the tumor will be summarized.

Physical performance and quality of life

Physical performance (ECOG and 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 9.3.1 and 9.5, respectively.

12. DATA MANAGEMENT

12.1. 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.

12.2. 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.

13. MONITORING PROCEDURES

13.1. 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.

14. 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 or for a period of 6 months.

14.1. 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 Terms are listed in Appendix B.

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.

14.2. 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 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 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 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 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 or study device.
 - If there is a valid reason to suspect a causal relationship between the AE and the procedure or study device, the AE should be considered "related or possibly related" to the procedure or study device.
- Outcome
- Action Taken

14.3. 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.

A Galil Medical clinical representative will work with the investigator to complete the SAE report. 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.

14.4. Grading of Toxicity

Grading of toxicity will be done according to Common Terminology Criteria for Adverse Events (CTCAE, version 4.0). See anticipated adverse events in Appendix B.

15. 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	[REDACTED]
Europe	[REDACTED]
Israel	[REDACTED]

16. INVESTIGATOR REQUIREMENT

16.1. 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 Certificate(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.

16.2. 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 IRB/IEC. If a modified ICF is used, 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.

16.3. Institutional Review Board/Independent Ethics Committee

This protocol, the Informed Consent Form (ICF) and relevant supporting information must be submitted to an Institutional Review Board / Independent Ethics Committee (IRB/IEC) before a site is initiated for participation. Approval from the IRB/IEC must be obtained before any 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.

16.4. Protocol Amendments

This protocol will only be altered by written amendments. Administrative changes that do not impact patient participation in the study 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.

16.5. 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.

17. STUDY COMMITTEE

17.1. 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.

18. STUDY ADMINISTRATION

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

18.1. Study Registration

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

18.2. 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

18.3. 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

19. 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.

20. 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.

21. 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).

22. REFERENCES

1. Goldfarb HA. Nd: YAG laser laparoscopic coagulation of symptomatic myomas. *J Rep Med*. 1993; 37: 636-638.
2. Phillips DR, Milim SJ, Nathanson HG, Hoselkorn J. Experience with laparoscopic leiomyoma coagulation and concomitant operative hysteroscopy. *J Am Assoc Gynecol Laparosc*. 1997; 4: 425-433.
3. Goldfarb HA. Laparoscopic coagulation of myomas (myolysis). *Obstet Gynecol Clin North Am*. 1995; 22: 807-819.
4. Cooper IS, Lee AS. Cryostatic congelation: A system for producing a limited, controlled region of cooling or freezing of biologic tissues. *J Nerv Ment Dis* 1961; 133: 259-263.
5. Saliken JC, Donnelly BJ, Rewcastle JC: The evolution and state of modern technology for prostate cryosurgery. *Urology* 2002; 60: 26-33.
6. Rewcastle JC, Sandison GA, Saliken JC, et al.: Considerations during clinical operation of two commercially available cryomachines. *J Surg Oncol* 1999; 71: 106-111.
7. Rewcastle JC, Hahn LJ, Saliken JC, et al.: Use of a moratorium to achieve consistent liquid nitrogen cryoprobe performance. *J Surg Oncol* 1997; 66: 10-113.
8. Gage AA. Current progress in cryosurgery. *Cryobiology* 1988; 25: 483-86.
9. Gage AA, Guest K, Montes M et al, Effect of varying freezing and thawing rates in experimental cryosurgery. *Cryobiology* 1985; 22: 175-182.
10. Gage AA. Progress in cryosurgery. *Cryobiology* 1992; 29: 300-34.
11. Gao XK, Sun DK, Sha RJ, Ding YS, et al. Precooled, spring-driven surgical cryoneedle: a new device for cryohaemorrhoidectomy. *Proceedings of the 11th International Cryogenic Engineering Conference, IECE 11, 1986. Berlin, West Germany. Pp. 825-54.*
12. Kollner P and Duczek E, Apparatus for cryosurgery. US Patent No. 3,794,039, 1974.
13. Homasson JP, Thierry JP, Angebault M et al. The operation and efficacy of cryosurgical, nitrous oxide-driven cryoprobe. *Cryobiology* 1994. 31: 290-304.
14. Hamilton A, Hu J. An electric cryoprobe for cryosurgery using heat pipes and thermoelectric coolers: a preliminary report. *J Med Eng & Tech* 1993; 17(3): 104-9.
15. Rabin Y, Julian TB, Wolmark N. A compact cryosurgical apparatus for minimal-invasive cryosurgery. *Biomed Instrument & Technol* 1997; 31: 251-258.
16. Rabin Y, Colman R, Mordohovich D, et al. A new cryosurgical device for controlled freezing. *Cryobiology* 1996; Part I: 33: 82-92, Part II: 33: 93-105.
17. Gage A, Baust M., and Baust J. Experimental cryosurgery investigations in vivo. *Cryobiology* 2009;59:229-243.
18. McTaggart R and Dupuy D. Thermal ablation of lung tumors. *Tech Vasc Interventional Rad* 2007;10:102-113.
19. Rand RW, Rand RP, Eggerding FA, et al. Cryolumpectomy for breast cancer: an experimental study. *Cryobiology* 1985; 22: 307-318.
20. Miller RH, Mazur P, Survival of frozen-thawed human red cells as a function of cooling and warming velocities. *Cryobiology* 1976; 13: 404-414.
21. DeVita, VT Jr, Hellman, S, Rosenberg S. *Cancer Principles & Practice of Oncology* 5th Edition. Vol 2:2536-2549.

22. Gómez FM, Palussière J, Santos E, Tourdias T, Cornélis F, Sáiz V, Montes H, Eker O. Radiofrequency thermocoagulation of lung tumours. Where we are, where we are headed. *Clin Transl Oncol.* 2009 Jan;11(1):28-34.
23. NCI. "What You Need to Know About Lung Cancer Booklet". 27 July 2007. <<http://www.cancer.gov/cancertopics/wyntk/lung>>.
24. Gillams A: Lung tumour ablation – where are we now. *Cancer Imaging.* 2008; 8: 116-117.
25. Ahmed A, Littrup PJ. Percutaneous Cryotherapy of the Thorax: Safety Considerations for Complex Cases. *AJR* 2006; 186:1703–1706.
26. Asimakopoulos G, Beeson J, Evans J, Maiwand MO. Cryosurgery for malignant endobronchial tumors: analysis of outcome. *Chest.* 2005 Jun;127(6):2007-14.
27. Kawamura M, Izumi Y, Tsukada N, Asakura K, Sugiura H, Yashiro H, Nakano K, Nakatsuka S, Kuribayashi S, Kobayashi K. Percutaneous cryoablation of small pulmonary malignant tumors under computed tomographic guidance with local anesthesia for nonsurgical candidates. *J Thorac Cardiovasc Surg.* 2006 May;131(5):1007-13.
28. Wang H, Littrup PJ, Duan Y, Zhang Y, Feng H, Nie Z. Thoracic Masses Treated with Percutaneous Cryotherapy: Initial Experience with More than 200 Procedures. *Vasc Interv Radiol.* 2005 April;235:289-298.
29. Goodwin PJ, Black JT, Bordeleau LJ, Ganz PA. Health-related quality-of-life measurement in randomized clinical trials in breast cancer-taking stock. *J Natl Cancer Inst* 2003; 95(4):263-281.
30. Moinpur CM, Hayden KA, Thompson IM. Quality of life assessment in Southwest Oncology Group trials. *Oncology* 1990; 4(89):79-84.
31. Blazeby JM, Avery K, Sprangers M, Pikhart H, Fayers P, Donovan J. Health-related quality of life measurement in randomized clinical trials in surgical oncology. *J Clin Oncol* 2006; 24(19):3178-3186.
32. Ware JE, Kosinski M, and Keller SD. A 12-Item Short-Form Health Survey: Construction of scales and preliminary tests of reliability and validity. *Medical Care,* 1996;34(3):220-233.

23. APPENDIX A: ABBREVIATIONS

Acronym	Definition
AE	Adverse Event
CDP	Clinical Discovery Platform
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
EDC	Electronic Data Capture
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
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
MRI	Magnetic Resonance Imaging
PCT	Percutaneous Cryotherapy
SAE	Serious Adverse Event
SF-12	Short Form – 12
UADE	Unanticipated Adverse Device Effect
XRT	External Beam Radiation

24. APPENDIX B: ANTICIPATED ADVERSE EVENTS AND CTCAE TERMS

ADVERSE EVENT	CTCAE TERM
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
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
Mucosal infection	Mucosal infection
Myocardial infarction	Myocardial infarction
Nausea	Nausea
Neuropathy: Sensory (e.g., lumbar	Peripheral sensory neuropathy

ADVERSE EVENT	CTCAE TERM
radiculopathy)	
Non-cardiac chest pain	Non-cardiac chest pain
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
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

ADVERSE EVENT	CTCAE TERM
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

25. APPENDIX C: PERFORMANCE STATUS SCORING (ECOG)

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

26. APPENDIX D: KARNOFSKY PERFORMANCE STATUS (KPS)

The Karnofsky Performance Scale Index 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

References:

Crooks, V, Waller S, et al. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. J Gerontol. 1991; 46: M139-M144.

de Haan R, Aaronson A, et al. Measuring quality of life in stroke. Stroke. 1993; 24:320- 327.

Hollen PJ, Gralla RJ, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. Cancer. 1994; 73: 2087-2098.

O'Toole DM, Golden AM. Evaluating cancer patients for rehabilitation potential. West J Med. 1991; 155:384-387.

Oxford Textbook of Palliative Medicine, Oxford University Press. 1993;109.

Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: Reliability, validity, and guidelines. J Clin Oncology. 1984; 2:187-193.

27. 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
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	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
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

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
	▼	▼	▼	▼	▼
a. <u>Accomplished less</u> than you would like	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b. Were limited in the <u>kind</u> of work or other activities	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

4. 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
	▼	▼	▼	▼	▼
a. <u>Accomplished less</u> than you would like	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b. Did work or other activities <u>less carefully than usual</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

5. 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
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

6. 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
	▼	▼	▼	▼	▼
a. Have you felt calm and peaceful?	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
b. Did you have a lot of energy?	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
c. Have you felt downhearted and depressed?	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

7. 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
▼	▼	▼	▼	▼
<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!