Detailed Protocol 2012p 001915

Title	**Percutaneous Image guided VATS resection of lung lesions**
Principal Investigator	**Raphael Bueno, MD rbueno@partners.org**
Study Coordinator	**Tamara Tilleman, MD/PhD ttilleman@partners.org** **221 Longwood Ave. Boston MA 1-617-505-5400**
Coordinating Center	**BWH**
Protocol Version Date	**01.29.14**

SCHEMA

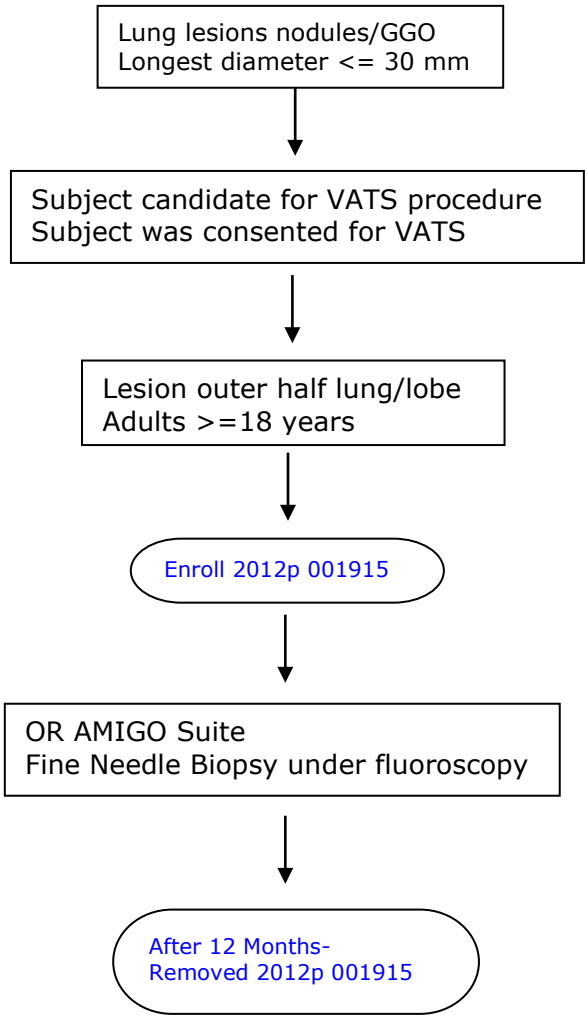

Lung lesions nodules/GGO
Longest diameter <= 30 mm
Subject candidate for VATS procedure
Subject was consented for VATS
Lesion outer half lung/lobe
Adults >=18 years
Enroll 2012p 001915
OR AMIGO Suite
Fine Needle Biopsy under fluoroscopy
After 12 Months-
Removed 2012p 001915

TABLE OF CONTENTS

*To update the Table of Contents, put your cursor in the Table of Contents and press **F9** to update it or **ctrl-a F9** to update all fields. When you update the Table of Contents, always choose to update the Entire Table.*

1. SPECIFIC AIMS

The purpose of this pilot clinical study is to test a methodology for using imaging by CT offered through the Advanced Multimodality Image Guided Operating (AMIGO) to guide an excisional biopsy of lung abnormalities identified by CT scans.

Our hypothesis is that an effective marking strategy of 3cm or smaller lung lesions, using intra-operative imaging-guidance, will enable accurate and efficient lesion resection while preserving as much as possible of the normal lung parenchyma by limiting the resection to the lesion and its immediate surrounding.

Our clinical initiative has 2 specific aims, one primary major and the other secondary taking advantage of this design:

Aim 1: To determine the feasibility of image guided VATS (Video Assisted Thoracoscopic Surgery) resection using real-time anatomical imaging modality for lung lesions/nodules. Specifically, we seek to establish the flow of the procedure and to determine the morbidity, success rate (as defined by complete resection), time from incision to closure of each procedure and radiation dose used in each procedure.

Aim 2: to determine whether molecular analysis of the lesion/nodule in conjunction with cytological analysis using FNAs (Fine Needle Aspirations) just prior to resection can predict diagnosis and prognosis.

2. BACKGROUND

Approximately 1,000,000 lung nodule and other abnormal lesions such as GGO (ground glass opacities) are detected in people in the United States each year. Lung nodules are found on 1 in 500 chest x-rays, and 1 in 100 CT scans of the chest. In reported studies, up to 51% of smokers aged 50 years or older have pulmonary nodules/lesions on CT scans.

A solitary pulmonary nodule is defined as a discrete, well-marginated, rounded opacity less than or equal to 3 cm in diameter that is completely surrounded by normal lung parenchyma, does not touch the hilum or mediastinum, and is without associated atelectasis or pleural effusion. GGO (Glass Ground Opacity) refers to specific changes in the lung parenchyma on CT that may represent tumor, pre-malignant lesion or other benign lung lesions.

Whether detected serendipitously or during a routine investigation, solitary pulmonary nodules/lesions pose a challenge to both clinicians and subjects[1]. A nodule on a chest radiograph raises several questions: Is the nodule benign or malignant? Should it be investigated or observed? Should it be surgically resected? The clinical context is also important and includes age, history of immunodeficiency (inherent or due to disease, chemoradiation, diabetes), travel history in endemic area for specific pulmonary pathogens (Ohio River valley, San Joaquim Valley, TB endemic areas), current infectious symptoms etc. In different clinical

circumstances the lesions/nodules can represent specific infections, benign growth, cancers or intrinsic pulmonary abnormalities.

Most solitary pulmonary nodules are benign. Seventy five percent of nodules less than 2 cm are benign [2] but they may represent an early stage of lung cancer. Lung cancer survival rates remain dismally low at 16% at 5 years [3,4]. If detected early enough, lung cancer can be treated and survival chances improved [5,6]. Early lung cancer, when the primary tumor is less than 3 cm in diameter (stage 1A or 1B), may lead to 5-year survival rates as high as 70-80%, yet only 15% of lung cancers are diagnosed at this early stage [3]. Likewise, a benign diagnosis can relieve patients from the radiation burden of follow up with CT scans and in some cases can provide a life saving treatment with steroids, antibiotics etc.

Recently, a large prospective randomized trial demonstrated that screening subjects at risk for lung cancer based on age and smoking history with chest computed tomography (CT) reduces the mortality from lung cancer [7,8]. The National Lung Screening Trial (NLST) involving more than 53,000 heavy smokers resulted in 20 percent fewer lung cancer deaths among trial participants who met specific criteria and were screened with low-dose helical CT [9]. As a consequence of this positive study, it is expected that hundreds of thousands of subjects with lung nodules/lesions will come to surgical biopsy. Statistically, the majority of these people will have benign diseases, but definitive diagnosis will be required in those with sufficiently large lesions or in radiographically suspicious lesions. Furthermore, subjects with very small lesions (<<1cm) that are suspicious for cancer will be discovered that are challenging to resection using current surgical techniques. Thus new protocols are required to improve resection accuracy, preserve normal lung and reduce morbidity, mortality and costs to society.

Based on clinical circumstances, lesions discovered on CT screening may be followed up radiographically or subjects may be referred for biopsy, radiological or surgical. The decision tree is based on size, appearance and clinical scenario (true for lesions suspected of either malignant or non-malignant etiologies). The protocol described herein, is designed for and limited to subjects who are referred for surgical biopsies.

Screening with computed tomographic (CT) scans has to some degree changed the technologies available for surgery for both lung cancers and for benign diseases. In the past and for most cases in the US currently (>75%), most lung cancers were relatively large and subjects required open thoracotomy for resection. Now-a-day, many cancers are much smaller and can be accessed through minimally invasive approaches, Video Assisted Thoracic Surgery (VATS) [10]. This is particularly the case in specialized centers such as BWH where most Thoracic Surgeons will attempt VATS resection for the majority of pulmonary nodules for any etiology. The same applies to non-cancerous nodules that need to be biopsied or resected for diagnosis and/or treatment. This surgery is routinely performed through 3 small incisions (1cm or so each) whereby one incision is used for the placement of a rigid video telescope camera and the other incisions are used to grab and mobilize the lung, bring it closer to one incision which will allow palpation of the lung with a finger tip

to identify the nodule/lesion that will then be cut out using a stapling device. We recently reviewed (unpublished results submitted for publication) all subjects aged 21-85 years who had surgical resection for small (≤ 2cm) non-small cell lung cancer at BWH from 2004-2008. Of 347subjects , 10.1% experienced ≥1 major complication and 16.1% a hospital stay of ≥1 week. The complications included: Adult respiratory distress syndrome (1), Aspiration (1), Bronchoplueral fistula (1), Cerebro vascular accident (1), Empyema (1), Myocardial infarction (1), Pulmonary edema (1), Pulmonary embolism (1), Ventilator for more than 7 days (1), Wound infection (1), Chylous leak (2), Tracheostomy (2), Acute renal failure (3), Atrial fibrillation (4), Re-operation due to bleeding (4), Re-intubation (5), Pneumonia (7), Air leak for at least 7 days (20). Of interest we also found that for a 30-minute increase in operative time, the odds of ≥ 1 major complication are estimated to increase by 103% (OR 2.03; 95% CI: 1.45-2.84), supporting the need to reduce operative time with a strategy such as proposed in this protocol. Though these complications and rates are only representative of one specific subset of our subjects they provide a highly relevant snap shot of rates and types of complications expected in this protocol.

The crux of the challenge and the reason for this protocol is that at surgery, many of these nodules/lesions are hard to palpate and to precisely define their location for resection. This is particularly true for smaller nodules or GGOs, precisely the ones that require resection to provide early diagnosis and therapy since at least half may be benign. Thus, using current technologies, which are non-image guided, result in three potential non-ideal outcomes: 1. A more extensive resection of normal lung parenchyma (such as lobectomy or segmentectomy) to make sure that the lesion is included even if it is non-palpable; 2. An enlargement of at least one incision to insert the hand into the chest for better physical definition-resulting in a more painful and complex recovery for the subject with resulting longer recovery, chronic pain and greater cost; 3. Too close a surgical margin to the cancer requiring re-operative surgery of increasing the chance of recurrence.

The concept of intra-operative imaging-guidance is not new and has been used for breast biopsy (needle localized breast biopsy) for many decades and more recently for neurosurgery. There are also a few reports in the literature using similar marking as for breast biopsies for lung lesions (using either a dye or the same coil as breast biopsies). The reports show that this is a safe and effective strategy [11-17]. However, the difference between what was previously reported in a few publications from what we propose herein is that the previous markings have been done at some time pre-operatively in a CT scanner as opposed to on the operating table with fluoro CT capabilities as available in AMIGO. The former approach limits the types of nodules that could be accessed because lack of general anesthesia and potential risk of pneumothorax which are eliminated in our protocol by having lung isolation already in place. Our approach is perform the -CT-guided marking directly in the operating room allowing for both marking and intra-operative tracking as required to ensure complete resection without moving the subject .

The AMIGO suite at BWH is an innovative operating room that allows for concurrent radiological imaging. It has a centralized, fully equipped and credentialed operating room with all the amenities as well as a fluoro-CT, movable MRI, Focused US and a PETCT area. The AMIGO suite is unique NIH funded resource for developing and perfecting novel surgical procedures which require imaging support. The intention is to develop these types of procedures in the AMIGO suite and then to modify them so that the successful procedures may be performed in the operating rooms. Parenthetically, an identical fluoro-CT is also available in one of the BWH operating rooms.

Our goal in this protocol is to enroll subjects who require VATS for specified lung lesions, have the subject be operated in the AMIGO suite where they undergo the following process: intubated with a double lumen tube, positioned in the lateral decubitus position, undergo CT- to confirm the location of the nodule, perform image guided needle biopsies and mark the lesion by placing a needle guided hookwire and/or T-bar. At this point, VAT surgery will be performed to resect the lung lesion utilizing the marking, which will remove the hookwire and/or T-bar with the specimen. The specimen will then be removed in an Endo-bag and submitted for a quick CT picture (away from the subject) and sent for pathological analysis. Only the underlined elements are experimental, the operation itself and indications are standard of care. The intentions are to define the methodology, risks, exposure etc. and then work in follow-up trials to potentially improve upon the marking device and the procedure to get them to the point where this approach is available for any subject undergoing lung resection. We believe that this is a game changing approach that is long overdue for thoracic surgery.

The second aim of this proposal takes advantage of the design of the protocol. In addition to placing an image guided marker, we propose to also obtain FNA from the lesion to be used for both cytological and molecular analysis. The results supporting this proposed aim come from our laboratory where through NCI funded projects we developed molecular tests based on gene expression strategies to distinguish normal lung from lung cancer [18] and mesothelioma from other cancers. We currently have a separate open clinical trial (with IRB approval) to obtain FNA biopsies under image guidance with ultrasound in subjects with mesothelioma (DFCI IRB protocol number 04-349). To-date about 115 subjects underwent this procedure with no complications [19].

The genetic analysis for this protocol involves taking the specimens obtained during the FNA procedure and using the RNA from these specimens to make cDNA. This cDNA will be used for transcriptional profiling and RNA sequencing. This will be done both in the tumor specimen as well as the adjacent normal specimen.

3. Participant SELECTION

Subject Selection:

This study will be initially limited to subjects with lung nodules or lesions 3cm or smaller in the outer half portion of the lung/lobe and who are candidate for VATS at

DFCI or BWH and consent for the procedure. The subjects will be formally consented at BWH only. The subjects may initially be told about the research procedure during a visit at DFCI with their thoracic surgeon, but if they choose to participate in the trial they will be consented at BWH. The CT will be reviewed by the study radiologist and thoracic surgeon prior to enrollment. At least 25 subjects scheduled for lung resection surgery will be enrolled to the study. The goal is 25 subjects who are enrolled into the trial.. All subjects will be chosen from the outpatient clinic of Thoracic Surgery, BWH.

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

- **Subjects Procedures** – subjects who are candidate for VATS and were consented for the procedure will be eligible for enrolled to the study.
- **Measurable Nodule** – lesions that are nodules/GGO or other abnormal opacity that can be accurately measured in at least one dimension with longest diameter <= 30 mm using conventional techniques.
- **Nodule Location** - lesions that are located in the outer half portion of the lung/lobe.
- **Enrolment Site** – Subjects who are seen at BWH and or DFCI Thoracic Surgery outpatient clinics. However, the subjects will formally consented at BWH only.
- **Age** – Enrollment at Partners will be limited to adults, 18 years and older.
- **Number of subjects** = 25 subjects will be enrolled to this stage of the study. Adult subjects, non-pregnant, non breast feeding to avoid radiation exposure. Urine and/or blood pregnancy test will be obtained based on clinical indications.

4. SUBJECT ENROLLMENT

We will use our clinical research standard operational procedures to recruit subjects ensuring that the confidentiality and privacy of potential subjects are protected. Potential subjects will be identified by their thoracic surgeon attending and other surgeon investigators during their visit to the outpatient clinic. These thoracic attendings have firsthand knowledge of the subject's medical history. The surgeon will evaluate and initially discuss the research with thesubject. If the subject agrees to participate in the research, the surgeon will obtain verbal consent from him/her to be contacted by the research staff. However, informed consent will be obtained by a licensed physician investigator.

Consent will be obtained by a licensed physician investigator at least a day prior to the start of the study procedures.
In addition:

- The CRA will ensure that subject identification is on all pages of the CF.
- There is documentation that the subject is given a copy of the consent form.
- Clinic research note documenting informed consent process.

- The subject and study representative signed and dated the consent form for him/herself.
- The subject initialed and dated all appropriate pages on the informed consent form.
- Note to file made for any informed consent deviations.
- The CRAs will ensure that a valid (current version date) copy of the consent form was used.
- Eligible participants will be registered in an enrollment log by the CRAs.
- Following registration, participants should begin protocol as soon as their procedure is scheduled. If a participant does not receive protocol treatment/procedure, the participant's protocol status will be changed (off-protocol)

5. STUDY PROCEDURE

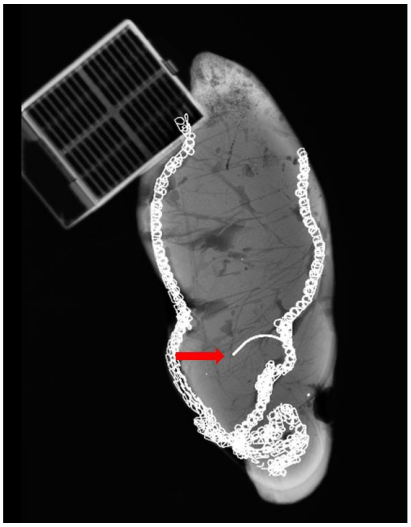
For Aim 1: To determine the feasibility of image guided VATS resection using AMIGO for lung lesions/nodules in subjects scheduled for lung resection surgery.

In practice, the subject will be placed under general anesthesia in an operating room with CT capabilities. The Advanced Multimodality Image Guided Operating (AMIGO) Suite is an innovative surgical and interventional environment that is the clinical translational test bed of the National Center for Image-Guided Therapy (NCIGT) at the Brigham and Women's Hospital (BWH) and Harvard Medical School. In AMIGO, real-time anatomical imaging modalities like x-ray and ultrasound are combined with cross sectional digital imaging systems like CT, MRI, and PET. There are two such rooms (with fluoro-CT) at the BWH currently, one in an AMIGO suite and the other being the hybrid operating room #1.

After the subject is asleep and appropriately positioned in lateral decubitus with a double lumen endotracheal tube in place, a brief image of the region of interest in the chest and or lung will be generated with the fluoro-CT and be fused with the preoperative CT (in this way minimizing exposure to radiation). Based on each subject's weight they will either receive their initial scan by Dyna-CT or by CT both of which are available in the AMIGO operating room suite. A needle will then be guided into the lesion under fluoroscopy, biopsies will be obtained and a hookwire and/or T-bar device will be placed through the needle, several needle passes may be required which is standard for image guided biopsies and localizations. The hookwire and/or T-bar are metallic objects that can be tracked with imaging and be used to precisely locate the lesion using imaging. Since it is better visualized on imaging than the original lesion, it is easier to track even when the lung is collapsed as it is in preparation for surgery. For the initial work in this protocol we proposed to use a hookwire and/or T-bar [Picture 1, 2, 3 and 4].
Each device is connected by a suture to the outside of the chest wall to allow constant guidance. Also, by visualizing the tract of the suture one can see where it enters the lung. Depending on the extent and location of the lesion one or two such devices may be placed (if needed to encompass the borders of the lesion). Once the device is placed, standard video assisted lung surgery will commence using 3-4 incisions, rigid video telescope camera and fluoroscopy if needed will guide the localization of the nodule. The lung around the nodule will then be grasped and resected with the hookwire and/or T-bar within it. The specimen will be then removed, investigated with imaging (away from the subject to avoid unnecessary radiation) to confirm that the original lung nodule/lesion is within and then taken to pathology to confirm that an abnormal nodule was resected and that the margins are appropriate, following our standard of care. The operation will then proceed and be concluded per standard of care.

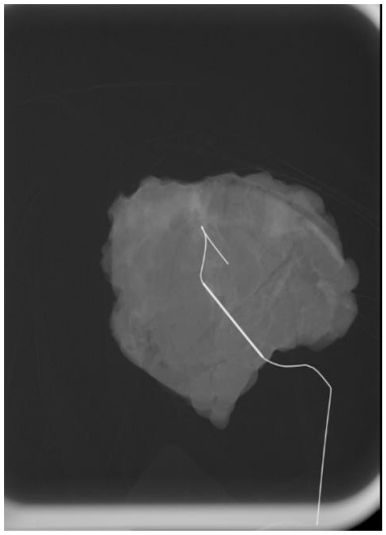
Picture 1, 2: Metallic Hookwire that can be tracked with imaging. In picture 1:

Human lung specimen (staples in the perimeter of the biopsy)- the tip of the Kopan's wire is market with red arrow



Picture 1

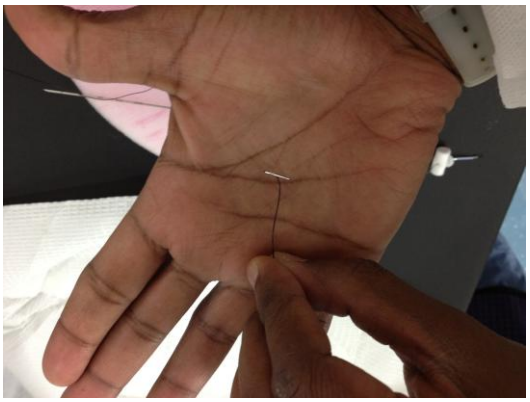
In picture 2: Wire in a breast tissue.



Resected Breast specimen radiograph with Kopan wire in it

Picture 2

In picture 3 and 4: Metallic T-bar that can be tracked with imaging.



For Aim 2: to determine whether molecular analysis of the nodule in conjunction with cytology using Fine Needle Aspirations FNAs can predict diagnosis and outcome. Aim 2 is based on preliminary work from our group showing that molecular analysis of FNA from thoracic lesions can provide accurate diagnosis. Since the subject will be in a position under general anesthesia to undergo needle placement of the hookwires and/or T-bar, we request permission for two more needle passes prior to it to obtain material for cytology and molecular testing to determine the diagnostic accuracy of combining the two. This is based on an approved protocol (DFCI 04-349 FINE NEEDLE BIOPSIES IN MPM) for which over 100 subject have been enrolled with no complications and diagnostic accuracy for mesothelioma of 93%. We anticipate that in this setting there should not be added risk to the subject .

Study endpoint: morbidity rate, 25subject .

5.1 Device

Metal wire, FDA approved like: Kopans Lesion Localization Hookwire.
http://fdazilla.com/fda/devices/search?q=hookwire

Metal T-bar, FDA approved like: Gastrointestinal Anchor Set with SaF-T-Pexy T-Fasteners by Kimberly-Clark Franklin, MA 02038 1-508-520-1328

5.2 Duration of Follow Up

Participants will be followed after removal from study for 12 months.

6. BIOSTATISTICIAN ANALYSIS

Percutaneous image-guided VATS resection of lung lesions will be considered to have acceptable morbidity if major complications were observed among 3 or fewer of the 25 subject total. The decision rule achieves 76% power to detect a 10% morbidity rate and accept the alternative hypothesis of non-inferiority of the protocol procedure. In contrast, the decision rule is associated with only 10% probability if the morbidity rate were truly 25% and thus unacceptably higher than the expected rate of 5-20%.

In order to protect the privacy and confidentiality of subjects, data retained in our research laboratories or sent to collaborators will be labeled with an alphanumeric code rather than with the subject's name, initials, medical record number, date of birth, or Social Security number.

6.1 Data Collection

Coded encounter data (diagnoses, procedures, dates)
Demographic data (age, gender, vital status)
Personal data (name, address, PCP)
Discharge Summary
History / Physical
History / Physical
Office / Clinic Notes
Medication List

Health / Medical Reports / Results including:
Blood Bank, Laboratory, Pathology, radiology

7. RISKS and DISCOMFORT

The risk to subject is considered relatively low. The major difference compared to standard care of either a percutaneous image guided biopsy or VAT surgery is the placement of the hookwire and/or T-bar and some added radiation anticipated but it is quite low. In addition, the entire needles track used to place the hookwires and/or T-bar will be removed during the resection of the lung nodule(s). The hookwires and/or T-bars will be tagged with a suture so that they are unlikely to disappear into thesubject .

The added amount of radiation you will be exposed to is from the additional x-ray exams, including fluoroscopy and CT scans. The amount of radiation you will receive will depend upon your body size rather than being a fixed amount. Depending on the number of image scans taken, the amount of radiation exposure you will receive is estimated to range between 5 to 30 millisieverts (mSv). A mSv is a unit of radiation dose. For comparison, everyone receives radiation exposure from natural background sources from the earth and the sky. The dose that you could receive from participation in this research study is about the same as you would normally receive in 1.5 to 10 years from these natural sources. Scientists disagree on whether radiation doses at these levels are harmful. A possible effect that could occur at doses associated with this study is a slight increase in the risk of developing cancer later in life.

8. POTENTIAL BENEFITS

Expected benefits to the individual subjects participating in the research: unlike many research protocols that do not provide clear subject benefit, we expect that this one will do so by allowing for:

1. Precise removal of the lesion with the minimum of lung parenchyma, preserving lung function.
2. Shorter operative time.
3. More likely to stay VATS resulting in smaller incisions as well as less pain and faster recovery.

9. MONITORING and QUALITY ASSURANCE

The Research Coordinators (CRAs) are responsible for compiling and submitting data collection for all participants and for providing the data to the Principal Investigator for review. The Research Coordinators will meet weekly and/or more often if required to review side effects and accrual data. Information to be reviewed: up-to-date participant accrual; all grade 2 or higher unexpected adverse events; summary of all deaths occurring within 7 days; summary of all deaths while being treated and during active follow-up; any audit results, and a summary provided by the study team.

The Principal Investigator (PI) will report to the IRB any of the following *unanticipated problems* and *adverse events* that occur: 1) during the conduct of the study, 2) after study completion, or 3) after subject withdrawal or completion. Any adverse events and unanticipated problems involving risks to subjects or other will be reported to the IRB per PHRC reporting guidelines. http://healthcare.partners.org/phsirb/Guidance/Reporting_Unanticipated_Problems_including_Adverse_Events.1.11.pdf

1. Internal adverse events that are unexpected, and related or possibly related to the research and that indicate there are new or increased risks to subjects;
2. External adverse events that are serious, unexpected, and related or possibly related to the research and that indicate there are new or increased risks to subjects that require some action (e.g., modification of the protocol, consent process, or informing subjects);
3. Unanticipated adverse device effects that are serious and caused by, or associated with, the device;
4. Deviation from the approved research protocol or plan without IRB approval in order to eliminate apparent immediate hazard to subjects or harm to others;
5. Deviation from the approved research protocol or plan that placed subjects or others at an increased risk of harm regardless of whether there was actual harm to subjects or others;
6. Any event that requires prompt reporting according to the research protocol or investigational plan or the sponsor;
7. Breach of confidentiality or violation of HIPAA (e.g., lost or stolen laptop);

8. Procedural or laboratory error (e.g., errors in surgical or other procedure, or testing of samples or test results) regardless of whether subjects experienced any harm;
9. Interim analysis, safety monitoring report, publication in a peer-reviewed journal, or other finding that indicates that there are new or increased risks to subject or others or that subjects are less likely to receive any direct benefits from the research.

As part of monitoring plan:

- CVs for all study staff are on file and updated every 2 years
- Medical licenses for the Co-Investigators are on file and updated prior to expiration
- Delegation Log is updated as new staff are added or removed from the study or new procedures are added
- Financial disclosures for PIs and those listed on the 1572 are on file
- All other essential documents have been prepared and completed as appropriate

10. REFERENCES

1. CT of the pulmonary nodule: a cooperative study. Zerhouni EA, Stitik FP, et al. Radiology. 1986 Aug;160(2):319-27.
2. CT Screening for Lung Cancer: Five-year Prospective Experience Stephen J. Swensen et al Radiology 2005;235:259-265.
3. Cancer Facts and Figures 2012: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf (last entered 8.6.2012)
4. United States Cancer Statistics (USCS), Cancer Death Rates (Table 4.1.M2). http://apps.nccd.cdc.gov/uscs/toptencancers.aspx (last entered 8.6.2012)
5. Lung cancer risk prediction to select smokers for screening CT- a model based on the Italian COSMOS trial. Maisonneuve P, Bagnardi V, Bellomi M, et al. Cancer Prev Res (Phila). 2011 Nov;4(11):1778-89. Epub 2011 Aug 2.
6. Lung cancer screening update. Bellomi M, Rampinelli C, De Fiori E, Preda L, Veronesi G. Cancer Imaging. 2009 Oct 2;9 Spec No A:S122-5. Diagnostic Radiology, European Institute of Oncology
7. The Danish randomized lung cancer CT screening trial--overall design and results of the prevalence round. Pedersen JH, Ashraf H, Dirksen A, et al. AJ Thorac Oncol. 2009 May;4(5):608-14.
8. Lung cancer screening with low-dose helical CT: results from the National Lung Screening Trial (NLST). Kramer BS, Berg CD, Aberle DR, Prorok PC. J Med Screen. 2011;18(3):109-11.
9. The National Lung Screening Trial: overview and study design.National Lung Screening Trial Research Team, Aberle DR, Berg CD, Black WC, et al. Radiology. 2011 Jan;258(1):243-53
10. Video-assisted thoracic surgery lobectomy: report of CALGB 39802--a prospective, multi-institution feasibility study. Swanson SJ, Herndon JE 2nd, D'Amico TA, et al. J Clin Oncol. 2007 Nov 1;25(31):4993-7.
11. Lung nodules in children: video-assisted thoracoscopic surgical resection after computed tomography-guided localization using a microcoil. Heran MK, Sangha BS, Mayo JR, Blair G, Skarsgard ED.J Pediatr Surg. 2011 Jun;46(6):1292-7. PMID: 21683242
12. Dual localization technique for thoracoscopic resection of lung lesions in children. Martin AE, Chen JY, Muratore CS, Mayo-Smith WW, Luks FI. J Laparoendosc Adv Surg Tech A. 2009 Apr;19 Suppl 1:S161-4. PMID: 18999984

13. Identification of small lung nodules: technique of radiotracer-guided thoracoscopic biopsy. Grogan EL, Jones DR, Kozower BD, Simmons WD, Daniel TM. Ann Thorac Surg. 2008 Feb;85(2):S772-7. PMID: 18222215
14. Needle localization for thoracoscopic resection of small pulmonary nodules in children. Waldhausen JH, Shaw DW, Hall DG, Sawin RS. J Pediatr Surg. 1997 Nov;32(11):1624-5. PMID: 9396541
15. Computer-tomographically guided fiberbronchoscopic transbronchial biopsy of small pulmonary lesions: a feasibility study. Wagner U, Walthers EM, Gelmetti W, Klose KJ, von Wichert P. Respiration. 1996;63(3):181-6. PMID: 8739490
16. CT-guided localizations of pulmonary nodules with methylene blue injections for thoracoscopic resections. Wicky S, Mayor B, Cuttat JF, Schnyder P. Chest. 1994 Nov;106(5):1326-8. PMID: 7956378
17. Localization of peripheral pulmonary nodules for thoracoscopic excision: value of CT-guided wire placement. Shah RM, Spirn PW, Salazar AM, Steiner RM, Cohn HE, Solit RW, Wechsler RJ, Erdman S. AJR Am J Roentgenol. 1993 Aug;161(2):279-83. PMID: 8333361
18. Differential diagnosis of Solitary lung nodules using gene expression ratios. J Thorac Cardiovasc Surg 2006; 132:621-7. PMID: 16935118. Gordon GJ, Deters LA, Nitz MD, Lieberman BC, Yeap BY, **Bueno R**.
19. Fine Needle Aspiration Biopsies for Gene Expression Ratio-based Diagnostic and Prognostic Tests in Malignant Pleural Mesothelioma. Clin Cancer Res. 2011:15;17(2):310-6. PMID: 21088255. De Rienzo A, Dong L, Beow YY, Jensen RV, Richards WG, Gordon G, Sugarbaker DJ, **Bueno R.**