MSK PROTOCOL COVER SHEET

Effect Of Autologous Blood Patch Injection Versus Biosentry Hydrogel Tract Plug In The Reduction Of Pneumothorax Risk Following Lung Biopsy Procedures

Amgad Moussa, MD/Radiology

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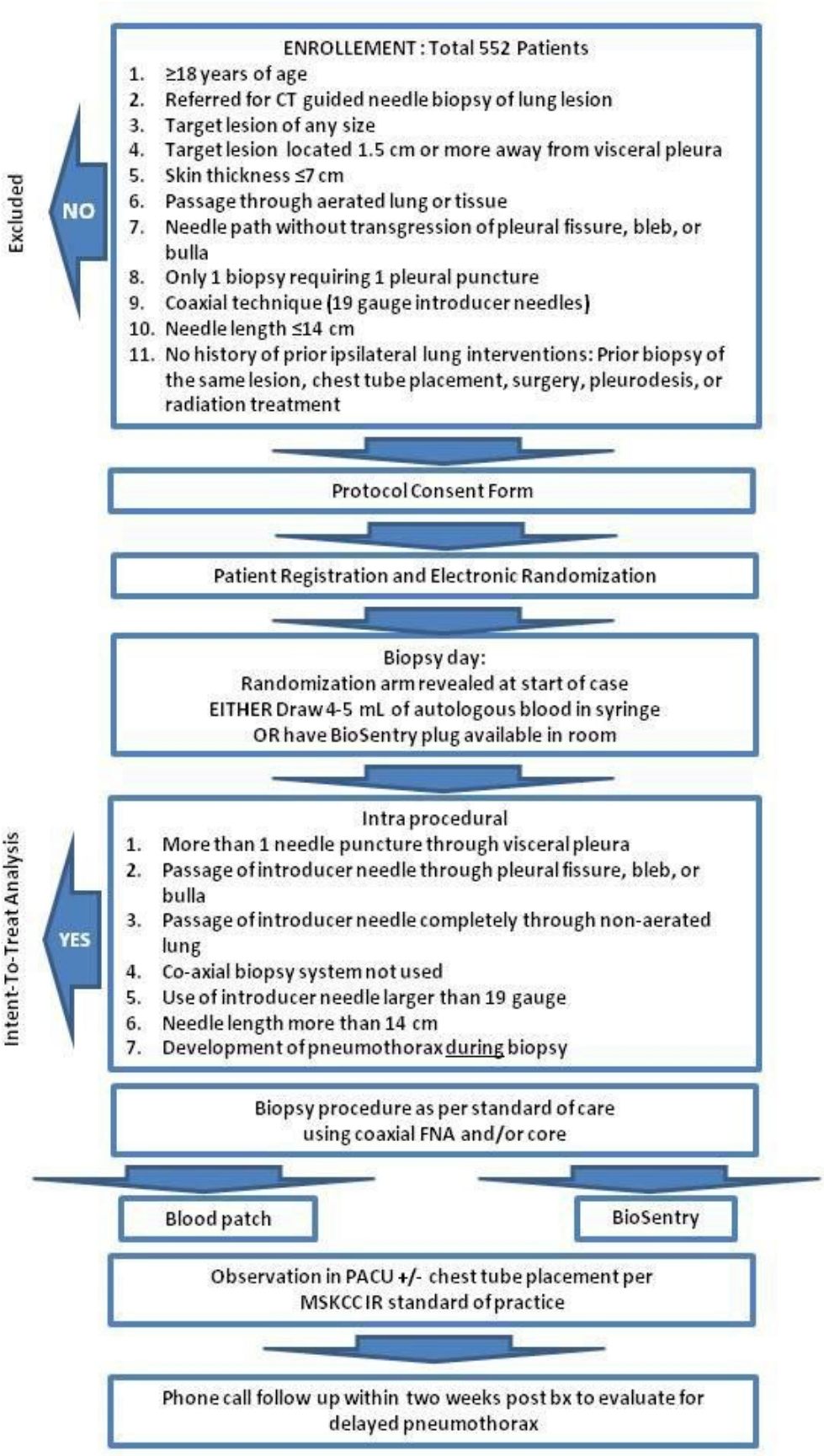
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This study will compare the effectiveness of autologous blood patch injection (ABPI) versus the BioSentry (formerly known as Bio-Seal) hydrogel Tract Plug (developed by Angiotech, Vancouver British Columbia) in reducing the rate of iatrogenic pneumothoraces when used in routine image guided lung biopsy procedures involving passage through aerated lungs. Both techniques are within the current standard of care in our institution. This involves the very last step of a lung biopsy which is removal of introducer needle. Patients who fulfill inclusion criteria will be randomized to one of two arms of the introducer needle removal technique. The patients will then be monitored in the post operative period for at least two hours with chest radiographs and any complications will be treated all as per standard of care practice. The vast majority of iatrogenic pneumothoraces from image guided lung biopsies occur within the first two hours post biopsy as determined by our own clinical experience [2] and confirmed by similar studies in the literature [3–5] . A follow up phone call (Appendix 20.4) to patients within two weeks after the lung biopsy is made to assess possible delayed pneumothoraces which are very rare and involve less than 1% of patients [2,3,5]. The phone call is not within standard of care. However any consequent treatments are within standard of care practice. We expect that less than 5 percent of all biopsies may end up being excluded during the procedure from intraprocedural complications precluding the use of a tract sealant.

The main objective is to determine non-inferiority of ABPI in the reduction of pneumothorax rate which is much cheaper to perform as opposed to BioSentry.

Potential candidates for this study will be recruited from patients referred to our Interventional Radiology service for lung biopsy.


ENROLLEMENT : Total 552 Patients
1. ≥18 years of age
2. Referred for CT guided needle biopsy of lung lesion
3. Target lesion of any size
4. Target lesion located 1.5 cm or more away from visceral pleura
5. Skin thickness ≤7 cm
6. Passage through aerated lung or tissue
7. Needle path without transgression of pleural fissure, bleb, or bulla
8. Only 1 biopsy requiring 1 pleural puncture
9. Coaxial technique (19 gauge introducer needles)
10. Needle length ≤14 cm
11. No history of prior ipsilateral lung interventions: Prior biopsy of the same lesion, chest tube placement, surgery, pleurodesis, or radiation treatment
Excluded
NO
Protocol Consent Form
Patient Registration and Electronic Randomization
Biopsy day:
Randomization arm revealed at start of case
EITHER Draw 4-5 mL of autologous blood in syringe
OR have BioSentry plug available in room
Intra procedural
1. More than 1 needle puncture through visceral pleura
2. Passage of introducer needle through pleural fissure, bleb, or bulla
3. Passage of introducer needle completely through non-aerated lung
4. Co-axial biopsy system not used
5. Use of introducer needle larger than 19 gauge
6. Needle length more than 14 cm
7. Development of pneumothorax during biopsy
Intent-To-Treat Analysis
YES
Biopsy procedure as per standard of care
using coaxial FNA and/or core
Blood patch
BioSentry
Observation in PACU +/- chest tube placement per
MSKCC IR standard of practice
Phone call follow up within two weeks post bx to evaluate for
delayed pneumothorax

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary objective:

- To determine non-inferiority of ABPI when compared to BioSentry in reducing the rate of iatrogenic pneumothorax during the routine observation stay within 2 hours following image guided lung biopsy.

Secondary objective:

- To evaluate ABPI and BioSentry in reducing the rate of iatrogenic pneumothorax during the routine observation stay within 2 hours following image guided biopsy in a per-protocol analysis.
- To evaluate ABPI and BioSentry in reducing the rate of chest tube placement for pneumothorax up to two weeks following lung biopsy.
- To evaluate ABPI and BioSentry in reducing the rate of delayed pneumothorax up to two weeks following lung biopsy.

3.0 BACKGROUND AND RATIONALE

Percutaneous needle biopsy of lung is a well accepted and accurate method of diagnosis of pulmonary nodules and masses (90 % sensitive; almost 100% specific for malignancy) [6–8]. The demand for percutaneous lung needle biopsies is on the rise given the rising incidence of lung cancer, increased detection of asymptomatic lung nodules on imaging and the need for tissue for new molecular diagnostics [9]. In 2012 IR service performed 1128 lung biopsies which resulted in 86 chest tube placements and consequent admissions (%7.2). The total number of lung biopsies has constantly increased over time at our institution. IR service currently performs around 100 lung biopsies each month. The most common complication of a percutaneous lung biopsy is pneumothorax [10] or lung collapse and is caused by air leaking out of the lung through needle puncture site on the visceral pleura once the needle is removed. This is determined clinically and is observed either on the final post procedure CT images or on the follow up chest radiographs performed within 2 hours of the procedure while the patient is still in the recovery room. The majority of iatrogenic pneumothoraces is small and managed conservatively but they may require intervention by either aspiration or placement of a chest tube which usually implies a hospital admission. Most large series report an incidence of 15-25% for iatrogenic pneumothorax, but in some studies, the rate can reach as high as 40% [10]. In our institution, the rate of post biopsy pneumothorax is estimated at 23% based on a study performed in 2004 which is close to the literature findings [1]. The risk of pneumothorax requiring intervention, chest tube placement and admission is smaller but nonetheless appreciable and reported risks range between 4% and 6% [10] similar to the rate we reported from our institution which is 6.8% [1]. There is no accurate method of predicting which patient will develop a pneumothorax or require chest tube placement although multiple factors such as chronic lung disease, small nodule size, increased depth from skin and needle gauge size have been shown to be contributing elements [1,11]. However, when these complications do occur, the psychological and economic burden can be significant. A study in 1998 by Gurley et al evaluated the cost of inpatient management of patients with chest tubes and found that the average total management costs amounted to $3,950 which was $2,261 more than that for outpatients

($1,689). The significant cost difference was found to be related primarily to the room charge, pharmacy charges, and the number of follow-up chest radiographs obtained during the inpatient hospital stay[12]. In our institution where the semi-private rate for inpatient hospital stay per day of stay is 4,180$, we expect these charges to be even higher reaching up to $10,342 of added cost when compared to biopsy patients who did not require a chest tube or admission. Given the rising need for biopsies, the relatively high incidence of iatrogenic pneumothoraces which can be potentially life-threatening and the high cost this particular complication incurs on healthcare resources when requiring treatment, there is great interest in techniques that reduce the occurrence of iatrogenic pneumothoraces. One such technique is the injection of certain materials into the biopsy path to close the puncture site, thus physically preventing air from leaking out into the pleural cavity. These materials have ranged from saline, to autologous blood, to manufactured plugs with varying results. The most popular of these have been the autologous blood patch and more recently a manufactured hydrogel plug called BioSentry [13]

An autologous blood patch consists of using the patient's coagulated blood to seal the puncture site at the end of a lung biopsy. The earliest report of its potential role in decreasing the incidence of pneumothorax was in 1988 where it was used in a limited number of patients, and though the results were not statistically significant, it did show a decrease in pneumothorax rate from 34.1% to 28% and a decrease in chest tube insertion rate from 9% to 7.7% [14]. Since then multiple other studies have evaluated the usefulness of the blood patch technique. Lang et al. showed a significant reduction in pneumothorax rate from 47% to 9% ($p<0.05$) in a study in 2000, and most recently in 2013, a randomized clinical trial was published in American Journal of Roentgenology (AJR) supporting the use of ABPI, mainly in reducing the rate of chest tube placement and admission from 18% to 9% ($p<0.05$) and similarly showing a trend in the reduction of pneumothorax rate from 35% to 26% ($p>0.05$)[15,16]. Following that same rationale, manufactured plugs have also been developed in recent years toward the same purpose. One such material is the BioSentry hydrogel plug developed by Angiotech and approved by FDA. BioSentry is deployed at the visceral pleural puncture site through the introducer needle using a deploying device (Figure 1). It swells upon contact with moisture and seals the pleural puncture site. It is absorbed by the patient's body over time. A supportive study of BioSentry by Zaetta et al. demonstrated a significant reduction of pneumothorax rate from 31% to 18%, and also a reduction –albeit non-significant- in the chest tube insertion rate from 11% to 4% compared to an untreated control group [13]. In an observation at our institution between 2007 and 2009, 181 consecutive patients undergoing lung biopsy by the author received blood patch. The rates of pneumothorax and chest tube placement, 6.6% (12/181) and 1.1% (2/181) respectively, were significantly lower than our group historical averages. Both of these techniques -either ABPI or BioSentry - along with "no plugging" are routinely used during lung biopsy procedures performed in our institution. Although both ABPI and BioSentry techniques have been independently validated in reducing the rate of pneumothorax and chest tube placement compared to controls, no head-to-head comparison has been made as to the effectiveness of these two techniques to justify the use of one over the other. There is no measurable added cost related to use of ABPI since the nursing personnel used in acquiring and handling the blood specimens are also involved in the patients' procedural sedation and thus perform these services within the scope of the procedure. Up to two standard stock syringes and

needles are used, the costs of which are negligible and lumped into the procedural costs. In comparison, the cost of a BioSentry device ranges around 200$ per device. Given the economic advantage of using ABPI in that it is almost free, it is of interest for us to prove that ABPI is at least as effective as manufactured plug in reducing pneumothorax and chest tube rates as they occur in our institution in order to justify its exclusive use.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This study will determine the rate of all pneumothoraces and those pneumothoraces requiring treatment following percutaneous lung biopsy in patients who have received ABPI or BioSentry at the end of the biopsy procedure. The data collected will be used to determine if there is equal effectiveness in the reduction of pneumothorax rates from both interventions.

4.3 Intervention

Patients with a focal lung lesion amenable to needle biopsy who meet initial inclusion criteria will be randomized and will report for their scheduled appointments as per standard practice. Once the patient arrives into the procedure room, the appropriate sealant technique will be prepared based on the assigned randomization arm. If the patient was randomized to the manufactured plug arm, the device will be made available at the start of the procedure. If the patient was randomized to the blood patch arm, then before the start of the procedure, phlebotomy will be performed, drawing 2-3 mL of the patient's blood into a labeled anticoagulant-free syringe which will be capped and left to clot in a cap-down position.

The specific anatomical site of the biopsy will be selected by the interventional radiologist. All standard protocol for lung biopsy will be followed routinely including NPO status, monitored sedation, and withholding of anticoagulation medications along with aspirin and clopidogrel bisulfate as per guidelines of MSKCC IR service. All biopsies will be performed using coaxial technique under CT guidance.

A limited CT scan of the lesion and adjacent lung parenchyma is acquired for biopsy planning. A biopsy path will be chosen to avoid pulmonary blebs, fissures, and pulmonary and superficial vessels, while the patient is positioned accordingly.

A biopsy path traversing at least 1.5 cm of aerated lung will be preferred so that an effective ABPI or BioSentry might be applied. Biopsies will be performed by any of the attending interventional radiologists or by an interventional radiology fellow under the direct supervision of an attending. A small sterile field is set. Local anesthesia will be used. An Angiotech 19-gauge introducer needle will be advanced into the corresponding lung with the needle tip at the near edge of the lesion. A 20-gauge automatic spring-loaded core biopsy gun (for example Temno, ACT) or a 20-22 Gauge FNA needle (for example Westcott) will be used to obtain core tissue and/or FNA samples. A cytotechnologist will be present on-site for all biopsies to assess adequacy of tissue samples as per standard of care.

Once the sample has been deemed adequate, and prior to removal of the guiding needle, the appropriate sealant technique will be delivered based on the patient's randomization arm.

If the patient was assigned to the ABPI group, a blood patch will be administered using the clotted blood in the syringe obtained at the beginning of the procedure. The guiding needle will be retracted up to 1.5-2 cm from the pleural surface, and the blood will be injected steadily and gently as the needle is pulled back out of the pleura. Injection will stop when the operator feels the needle is in subcutaneous tissues.

If the patient is assigned to BioSentry group, using the manufacturer's deployment device (Figure 1) the introducer needle is positioned so that the tip is at least 1.5 cm deep to the visceral pleura. The coaxial introducer needle hub will be prehydrated with a drop of saline, the BioSentry plug housing will be mated and locked to the hub and the plug will be deployed.

If during the biopsy procedure, there was onset of a pneumothorax before deployment of autologous or manufactured plug, or there was more than one pleural puncture, or passage through a fissure, a bleb, non aerated lung, the sealant may be administered if still technically feasible, and the decision will be at the discretion of the operator. If a coaxial system was not used, the sealant cannot be administered. These cases will be included in the primary intent-to-treat analysis, but excluded in a secondary per-protocol analysis:

- More than 1 needle pass through visceral pleura
- Passage of needle through pleural fissure, bleb, or bulla
- Passage of needle through consolidated or non-aerated lung
- Co-axial biopsy system not used
- Development of pneumothorax before deployment of BioSentry or ABPI
- Use of introducer needle larger than 19 gauge
- Needle length more than 15 cm

We expect that less than 5 percent of all biopsies may end up being excluded during the procedure from intraprocedural complications precluding the use of a tract sealant.

After the procedure, all patients will be transferred to the recovery unit where at least two chest radiographs will be obtained immediately and 2 hours after the procedure according to standard of care. Additional radiographs may be obtained if indicated according to standard of care.

The post procedure chest radiographs will be evaluated by the biopsy operator for the presence of pneumothorax which will appear as free air collection overlying the lung parenchyma inside the chest wall. A Pneumothorax is generated from air leaking from the needle puncture site into the visceral pleura. Patients with no or small stable asymptomatic pneumothoraces will be discharged.

A chest tube will be placed for patients with a large pneumothorax, patients with a pneumothorax that is increasing in size, or symptomatic patients with potentially any size pneumothorax on post procedure chest radiographs. Most patients who undergo chest tube placement will be admitted for overnight observation. Chest tubes will be removed when there is no longer an air leak and the radiographic appearance remains stable for 2 hours

with the chest tube clamped. This happens the next day of the biopsy for the majority of cases. Patients will be discharged home once the chest tube is removed. At the time of discharge all patients will be given contact information and will be asked to call back with any symptoms that might be related to delayed pneumothorax. In addition, patients who do not have a chest tube placed will be also followed up with a phone call by a member of IR service at one week checking for delayed pneumothorax (appendix 20.4). In case any of the study patients present with symptomatic or incidental delayed pneumothorax after being discharged, these patients' data will be captured for analysis. This phone call is the only part of this study which is not a part of standard of care however any consequent interventions based on the phone call are within standard of care practice.

All biopsy chest radiographs and CT images will be analyzed by the radiologist performing the procedure to identify emphysema (appendix 20.2.2) if present. .The prescan images, as well as any recent chest CT studies, if available, will be examined in lung windows on the PACS workstation. The lung parenchyma surrounding the lesion and in the region of the biopsy needle course will be analyzed for emphysema, blebs and transfissural approach.

Pneumothorax (appendix 20.2.1) will be mainly defined based on post procedure chest x-rays. Any discernible pneumothorax on chest x-rays is considered a positive finding. Miniscule pneumothorax (a tiny film of air) which is sometimes seen on the last set of CT images of a biopsy procedure after the introducer needle is removed is not considered a positive finding. This is due to high sensitivity of CT imaging. Any pneumothorax larger than miniscule on CT images is considered a positive finding.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

The BioSentry Biopsy Tract Plug (Angiotech Pharmaceuticals, Inc. Vancouver, Canada; Figure 1, Appendix 20.1), is a hydrogel based tract sealant which has been FDA approved to be used through standard Angiotech 19 gauge coaxial needles. It can be made currently available in stock for routine use during lung biopsy procedures.

An autologous blood patch injection (ABPI) consists of drawing 2-3 mL of the patient's blood prior to the procedure and leaving it in a sterile syringe to clot, then using the patient's coagulated blood to seal the puncture site at the end of a lung biopsy. This technique can be used through 19 gauge needles.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- ≥18 years of age
- Referred for CT guided biopsy of lung lesion
- Target lesion of any size
- Target lesion located 1.5 cm or more away from visceral pleura based on the needle path
- Skin thickness ≤7 cm (from skin to pleura)
- Needle path without transgression of pleural fissure, bleb, or bulla is possible
- Coaxial biopsy technique using Angiotech 19-Gauge introducer needle

- Needle length ≤15 cm

6.3 Subject Exclusion Criteria

- Preprocedural exclusion criteria
  - Passage through non-aerated lung or tissue
  - More than 1 biopsy on the same side requiring more than 1 pleural puncture
  - History of prior ipsilateral lung interventions including:
    - Chest tube placement
    - Surgery
    - Pleurodesis
    - Radiation treatment

7.0 RECRUITMENT PLAN

The subjects of this study will be identified and recruited by members of the Interventional Radiology service through referrals for lung biopsy. There will be no selection preferences based on age, gender, race, indication or target lesion characteristics. The patients will be selected initially based on the inclusion criteria outlined above and also based on appropriate clinical history as outlined in the exclusion criteria. This process will be conducted during the patient's visit to the interventional radiology clinic or in the inpatient unit prior to the patient's biopsy. The interventional radiologist performing the clinic evaluation or procedure consent will determine eligibility of the patient and discuss potential enrollment in the study. Subjects recruited as inpatients will be consented to the protocol and biopsy on the inpatient floor about an hour prior to the procedure. As these biopsies are not planned in advance, the time between ordering and performing the biopsy is minimal. The consenting professional will give ample time for discussion and questions.

All parameters related to the study are collected by treating IR physicians in Physicians Data Form for each patient (Appendix 20.3).

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process.The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information

relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

During a biopsy procedure, less than ideal conditions may occur such as outlined above that may affect clinical outcome. In this case deployment of blood patch or plug may still proceed at the performing physician's discretion, and the patient will be included in the intent-to-treat analysis.

The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained in a secure database as part of a screening log. The screening log will be maintained in order to ensure that patients who do not wish to participate are not approached again.

8.0 PRETREATMENT EVALUATION

No additional pretreatment evaluation will be necessary other than those required for the lung biopsy procedure as per standard of care. These include pre-procedure imaging and routine blood tests such as Prothrombin Time, INR, Platelet counts, WBC and pre-surgical testing if deemed necessary by the treating physician. Depending on the type of medications, non-steroidal anti inflammatory drugs, anti platelet agents and anticoagulants are held from 1-5 days from the date of biopsy.

9.0 TREATMENT/INTERVENTION PLAN

Both ABPI and the BioSentry are being used during routine lung biopsy procedures in MSKCC IR service although inconsistently, with preferences and usages varying among practitioners. Candidates enrolled in the study will selectively receive one or the other intervention as part of standard treatment protocol during lung biopsy procedures. Either one of these interventions is considered as an equivalent standard of care, and no additional fees should be incurred for the sole purpose of research.

Randomization will be done electronically after patient registration. Either the blood patch will be drawn or the BioSentry device will be made available at the start of the procedure in the IR room based on the randomization arm. If the patient was assigned to the ABPI group, a blood patch will be administered using the clotted blood in the labeled syringe obtained at the beginning of the procedure. The guiding needle will be retracted up to 2 cm from the pleural surface, and the blood will be injected slowly and steadily as the needle is pulled back out of the pleura.

If the patient is assigned to the BioSentry group, using the manufacturer's deployment system the introducer needle is positioned so that the tip is at least 1.5 cm deep to the visceral pleura. The coaxial introducer needle hub will be prehydrated with a drop of saline, and the tract plug housing will be mated and locked to the hub. The plug will be deployed.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

After the biopsy, the patient will be transferred to the recovery unit. Two chest radiographs will be obtained immediately and 2 hours after the procedure as per standard of care. Additional radiographs may be obtained when indicated as per standard of care.

Patients with no or with a small stable asymptomatic pneumothorax on the post procedure chest radiographs will be discharged.

A chest tube will be placed for patients with a large pneumothorax, patients with a pneumothorax that is increasing in size rapidly, or symptomatic patients with any pneumothorax. Patients who undergo chest tube placement will generally be admitted for overnight observation. Chest tubes will be removed when there is no longer an air leak and the radiographic appearance remains stable for 2 hours with the chest tube clamped. This happens the next day of the biopsy for the majority of cases. Patients will be discharged home once the chest tube is removed. At the time of discharge all patients will be given contact information and will be asked to call back with any symptoms that might be related to delayed pneumothorax. In addition, patients who did not have a chest tube placed will be followed up with a phone call within two weeks for assessment of delayed pneumothorax, a rare occurrence. The only step in the peri, intra and post procedural management of these patients which is not a part of standard of care is the one-week post procedure phone call. All other steps are within standard of care. Any treatment as a consequence to the follow-up phone call is also a part of standard of care.

In case any of the study patients present with symptomatic or incidental delayed pneumothorax after being discharged, these patients will be captured for analysis.

To help keep impartiality, in addition to the standard of care review of post biopsy chest x-rays, at a later time, all chest radiographs will be reviewed by an interventional radiologist who was not involved with the biopsy procedure and is unaware of the randomization arm. All disagreements will be solved based on consensus after a third impartial interventional radiologist reviews the images.

11.0 TOXICITIES/SIDE EFFECTS

There are no anticipated additional side effects to the intervention other than those expected during regular lung biopsy procedures.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Lack of any detectable pneumothorax as visualized on post procedure chest radiographs at 2 hours following the procedure is considered success. The rate of any pneumothorax that did not require treatment as well as those which require chest tube placement will be captured for analysis in each group.

Lack of prospective follow up chest x-ray at one week after biopsy will lower the accuracy of the study due to suboptimal capturing of delayed pneumothoraces by a phone call although this number is expected to be very low. For patients that are unable to be reached or unable to complete the follow up phone call, the incidence of a delayed pneumothorax and/or chest tube placement will be determined by a review of the patient's chart by the PI in the 2 weeks following the lung biopsy.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patient exclusion will be performed after chart review and interview. Patients will be excluded from the study in the event the patient was found to have a history of prior ipsilateral lung intervention as outlined above. Once randomized, patients will be included in the intent to treat analysis whether they received a blood patch/BioSentry plug or not.

14.0 BIOSTATISTICS

This is a randomized trial comparing autologous blood patch injection with BioSentry on the rate of pneumothorax after percutaneous lung biopsy. The primary endpoint is the rate of pneumothorax within 2 hours following biopsy. Pneumothorax is observed on post procedure CT scan or on follow-up chest radiographs while the patient is in the recovery room, according to standard of care.

This study will have a non-inferiority design to evaluate whether ABPI is associated with less than a 10% increase in pneumothorax rate compared to BioSentry. We will test the null hypothesis that ABPI is inferior, with a 10% or more increase in pneumothorax rate compared to BioSentry. The non-inferiority margin of 10% is considered clinically acceptable. Allowing for 1 interim assessment, the study will require 276 patients in each arm (552 patients total) to have 90% power to test this hypothesis. This sample size estimate assumes the pneumothorax rate with tract plug is approximately 20% based on a randomized study by Zaetta et al. An interim assessment will be performed after approximately half the patients (roughly 276 patients) have been enrolled onto the study. Using the Lan-DeMets spending function, the trial will terminate early for non-inferiority if with half the patients, a one-sided nominal Z-score of -2.538 (p-value ≤ 0.0056) is observed. This nominal z-score will be recalculated based on the available exact information fraction at the time of the Data Safety Monitoring Board review. If the trial continues, the final assessment will use a Z-score of -1.662 with an associated p-value of 0.0482. This preserves a 5% overall probability (1-sided type I error) of falsely concluding that ABPI is non-inferior to tract plug when it is truly worse. In 2012 IR service performed 1128 lung biopsies. IR service currently performs around 100 lung biopsies each month. With an anticipated eligibility rate of 50%, this study will take up to 24 months.

All randomized patients who undergo a biopsy will be analyzed for the primary outcome on a modified intent-to-treat basis according to the randomized treatment assignment regardless of the actual intervention received. The difference between pneumothorax rates for ABPI and BioSentry will be estimated and assessed using a Z-test. The same analysis method will be used to perform a secondary analysis on only patients who have a sealant placed after their biopsy.

Secondary outcomes will include comparisons of ABPI with BioSentry on 1) delayed pneumothorax occurring after outpatient observation stay and within 2 weeks following lung biopsy, and 2) pneumothorax requiring chest tube placement up to 2 weeks following lung

biopsy. These outcomes will be assessed in a similar manner to the primary outcome. For patients that are unable to be reached or unable to complete the follow up phone call, the incidence of a delayed pneumothorax and/or chest tube placement will be determined by a review of the patient's chart by the PI in the 2 weeks following the lung biopsy.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.3 Randomization

Patients will be randomized to receive either ABPI or BioSentry. Randomization will be done electronically using the Clinical Research Database (CRDB) after patient registration. Either the blood patch will be drawn or the BioSentry device will be made available at the start of the procedure in the IR room based on the randomization arm. Randomization will be accomplished by the method of random permuted block.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant/RSA will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will

be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for it's level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Risks to Subjects

Human Subjects Involvement and Characteristics: All patients at MSKCC who meet the inclusion criteria will be eligible. Patients will be 18 years of age or older. Both men and women and members of all ethnic groups are eligible for this trial. Pregnant and breast-feeding women are excluded from this study. This protocol does not include children because the number of children is expected to be limited for the patient population expected to be accrued onto this study. Also, the majority of children are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

Adequacy of protection against risks

Participation in the trial is voluntary.

Possible Toxicities/Side-Effects: The risks of biopsy are described in the informed consent and in Section 8.0. There is no known additional toxicities/side effects related to any of the two techniques.

Costs: The cost of the study does not exceed standard treatment costs.

Alternatives: The alternative to this trial would be use of either sealant technique versus no use of sealant at the discretion of the treating physician.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other appropriate personnel (e.g. qualified monitors from MSKCC) may review patient records as required.

Patient safety: Patients are monitored by physicians and nurses who are very familiar with lung biopsy procedures. In the case of an adverse reaction, immediate medical attention is available. In the evenings and weekends, we have a 24-hour urgent care facility for outpatients. The PI or co-PI will also be available at all times to organize any necessary intervention.

Monitoring of data to ensure safety: This study is to be monitored by the institutional IRB. This incorporates an independent data and safety monitoring board established by arrangement with the National Cancer Institute. The analysis of safety will include all patients. Adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by severity and causality.

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. We realize that patients may be hospitalized for reasons related to their cancer. As such, we will only report Grades 4 and 5 adverse events such as infection, bleeding, etc. that are thought to be possibly, probably, or definitely related to either sealant technique. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. Consent for lung biopsy is separate than the consent for this protocol. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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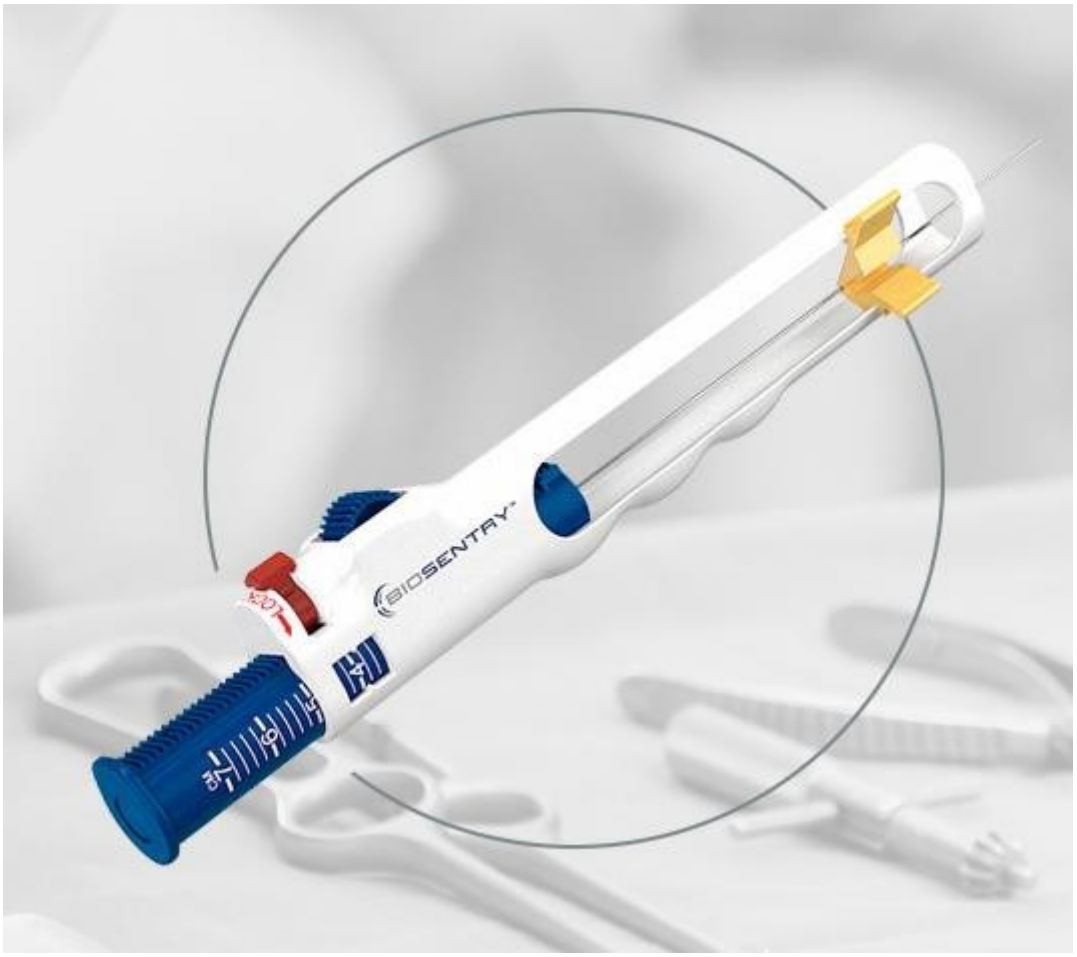
20.1 APPENDICES

20.2 FIGURES

Figure 1: The BioSentry Lung Biopsy Tract Plug



20.3 DEFINITIONS

Adapted from:

Grainger RG, Allison D, Adam A et al. Grainger's and Allison's Diagnostic Radiology, A Textbook of Medical Imaging. Philadelphia : Churchill Livingstone Elsevier, 2008.; 2008.

Dähnert W. Radiology Review Manual. Lippincott Williams & Wilkins; 2011.

20.3.1 PNEUMOTHORAX

Pneumothorax is defined as the accumulation of air in the pleural space causing lung collapse. The degree of pneumothorax and subsequent lung collapse can range from mild requiring no intervention to severe requiring evacuation of the air in the pleural space by placement of a chest tube. Pneumothorax can be associated with back, shoulder pain or shortness of breath. The diagnosis of pneumothorax in our study will be made with the chest

radiograph, which also detects complications and predisposing conditions and helps in management. These are seen on an erect or semi-erect radiographs in which the pleural air rises to the lung apex, in more severe cases it might become circumferential. Under these conditions the visceral pleural line becomes separated from the chest wall by a transradiant zone devoid of vessels.

Other signs that suggest a pneumothorax on a chest radiograph are:

- ipsilateral transradiancy, either generalized or hypochondrial
- a deep, finger-like costophrenic sulcus laterally
- a visible anterior costophrenic recess seen as an oblique line or interface in the hypochondrium; when the recess is manifest as an interface it mimics the adjacent diaphragm ('double diaphragm sign')
- a transradiant band parallel to the diaphragm and/or mediastinum with undue clarity of the mediastinal border
- visualization of the undersurface of the heart, and of the cardiac fat pads as rounded opacities suggesting masses
- diaphragm depression.

A large pneumothorax can potentially lead to tension pneumothorax. When intrapleural pressure becomes positive relative to atmospheric pressure for a significant part of the respiratory cycle it can impair gas exchange and cardiovascular function and eventually lead to life threatening respiratory distress. Ideally, evacuation of the air in the pleural space by placement of a chest tube is performed before onset of a tension pneumothorax. A pneumothorax is targeted for treatment when it is considered to be occupying more than 20-30% of the pleural space. At this stage, pneumothoraces may still be asymptomatic yet are large enough to accommodate placement of a chest tube. A smaller pneumothorax may be treated if it is associated with one or all of the symptoms described above. The chest tube is usually connected to a water-seal device to allow escape but prevent reflux of air into the pleural space.

20.3.2 EMPHYSEMA

Emphysema is defined as a condition of the lung characterized by permanent, abnormal enlargement of airspaces distal to the terminal bronchioles, accompanied by the destruction of their walls without obvious fibrosis. The most important aetiological factor by far is cigarette smoking. Emphysema is thought to result from the destruction of elastic fibres caused by an imbalance between proteases and protease inhibitors in the lung and from the mechanical stresses of ventilation and coughing. Proteases are normally released in low concentration by phagocytes in the lung. Tobacco smoke increases the number of pulmonary macrophages and neutrophils, reduces antiprotease activity, and may impair the synthesis of elastin. As emphysema develops lung destruction progresses, airspaces enlarge and elastic recoil declines. This, in turn, renders the lungs more vulnerable to injury from needle biopsies due to increased friability, and more prone to air leaks due to the larger airspaces.

Radiographic findings

The main radiographic manifestations of emphysema are overinflation and alterations in the lung vessels. Signs of overinflation are the best predictors of the presence and severity of emphysema. Signs of overinflation include the height of the right lung being greater than 29.9 cm, location of the right hemidiaphragm at or below the anterior aspect of the seventh rib, flattening of the hemidiaphragm, enlargement of the retrosternal space, widening of the sternodiaphragmatic angle and narrowing of the transverse cardiac diameter). Alterations in lung vessels include arterial depletion, whereas vessels of normal, or occasionally increased, calibre are present in unaffected areas of the lung, absence or displacement of vessels caused by bullae, widened branching angles with loss of side branches and vascular redistribution. Bullae are much more common in the upper zones, but the distribution can be much more even.

20.4 PHYSICIAN DATA FORM

Effect of Autologous Blood Patch Injection versus BioSentry hydrogel Tract Plug in the reduction of pneumothorax risk following lung biopsy procedures

1- Patient Demographics

MRN	Procedure date / /	
Last Name	Male Female	DOB / /

2- Candidate for study Yes No

If no, please explain why or list/circle exclusion criteria #:

3- Consent obtained Yes No

4- Randomization # _____

Exclusion criteria
1. Passage through non-aerated lung or tissue OR Target lesion located LESS than 1.5 cm away from visceral pleura
2. Needle path transgressing pleural fissure or bleb
3. Coaxial technique not needed
4. Needle size 17 gauge
5. Prior ipsilateral lung interventions: biopsy, chest tube, surgery, radiation or pleurodesis

5- Procedure parameters

Target size (largest transverse diameter on reference image) _____cm

Target depth (Needle path distance from pleura to outer edge of target) _____cm

Lobe (please circle) RUL RML RLL LUL LLL

Patient position (please circle) Supine Prone Other:

Type of biopsy (please circle) FNA Core Both

Number of biopsy samples FNA: Core:

6- Factors affecting outcome: Did you encounter (please circle)

More than 1 pleural puncture? Yes No

Passage through a fissure? Yes No

Complete passage through non aerated lung? Yes No

Passage through a bleb/bulla? Yes No

Usage of BARE needle WITHOUT coaxial system? Yes No

Intraprocedural pneumothorax? Yes No

Significant needle path hemorrhage within 2 cm of pleura? Yes No

7- Sealant technique used (please circle) Blood patch BioSentry None
(Please note reason below)

8- Outcomes

Pneumothorax on CXR (please circle) Yes No

Pneumothorax - Second reader (please circle) Yes No

Chest tube placement (please circle) Yes No

Delayed complications (please circle) Yes No If Yes: _____

Notes:

Thank you very much for your help and valuable input. For any questions regarding the protocol or questionnaire, you can reach Nadim Muallem on pager 8239 or muallemn@mskcc.org