

Safety of investigative bronchoscopy in the Severe Asthma Research Program

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Background: Investigative bronchoscopy was performed in a subset of participants in the Severe Asthma Research Program to gain insights into the pathobiology of severe disease. We evaluated the safety aspects of this procedure in this cohort with specific focus on patients with severe asthma.

Objective: To evaluate prospectively changes in lung function and the frequency of adverse events related to investigative bronchoscopy.

Methods: Bronchoscopy was performed by using a common manual of procedures. A subset of very severe asthma was defined by severe airflow obstruction, chronic oral corticosteroid use, and recent asthma exacerbations. Subjects were monitored for changes in lung function and contacted by telephone for 3 days after the procedure.

Results: A total of 436 subjects underwent bronchoscopy (97 normal, 196 not severe, 102 severe, and 41 very severe asthma). Nine subjects were evaluated in hospital settings after

bronchoscopy; 7 of these were respiratory-related events. Recent emergency department visits, chronic oral corticosteroid use, and a history of pneumonia were more frequent in subjects who had asthma exacerbations after bronchoscopy. The fall in FEV₁ after bronchoscopy was similar in the severe and milder asthma groups. Prebronchodilator FEV₁ was the strongest predictor of change in FEV₁ after bronchoscopy with larger decreases observed in subjects with better lung function.

Conclusion: Bronchoscopy in subjects with severe asthma was well tolerated. Asthma exacerbations were rare, and reduction in pulmonary function after the procedure was similar to that in subjects with less severe asthma. With proper precautions, investigative bronchoscopy can be performed safely in severe asthma. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: Investigative bronchoscopy, safety, severe asthma, exacerbation

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Abbreviations used

ATS:	American Thoracic Society
BAL:	Bronchoalveolar lavage
BMI:	Body mass index
DSMB:	Data safety monitoring board
ED:	Emergency department
HCU:	Health care utilization
MoP:	Severe Asthma Research Program Manual of Procedures
SARP:	Severe Asthma Research Program
VSA:	Very severe asthma

Airway inflammation is a central component of asthma.^{1,2} Bronchoscopy has provided an investigative approach to obtain airway fluids and mucosal biopsies, which has been critical to demonstrate the pattern and persistence of inflammation in asthma and begin to identify the link between these features and altered pathophysiology. Investigative bronchoscopy has provided a major step forward to understand more fully airway mechanisms of asthma as these studies focus on the target organ of disease, the lung.^{3,4} To date, the majority of bronchoscopy studies have been performed in patients with mild to moderate disease. Severe asthma remains poorly understood and is a phenotype of asthma with greater morbidity. Extending investigative bronchoscopy to patients with more severe disease promises to provide a critical opportunity to gain novel insight into what is anticipated to be a unique histopathology. It may provide clues to what causes greater severity in this population, and act as a stimulus to the development of more effective therapeutic interventions.

The lack of data assessing the safety of investigative bronchoscopy in patients with more severe asthma has been a limitation in the use of this research technique to understand better the pathophysiology of severe disease.⁵ There are few published studies evaluating the safety of investigative bronchoscopy in asthma and the effects of this procedure on physiologic changes, and even fewer on the effects of the procedure on short-term asthma control.⁶⁻¹¹ Collectively, only a small number of subjects with asthma and severe airflow obstruction have been included in previous studies, and most patients were not being treated with high doses of inhaled or oral corticosteroids at the time of the bronchoscopy.

In 2001, the National Heart, Lung, and Blood Institute established the Severe Asthma Research Program (SARP) at 9 sites in the United States and 1 in the United Kingdom. A major goal of the SARP was to identify and characterize a large number of subjects with severe asthma to establish the clinical characteristics of severe disease and understand pathobiologic mechanisms important in severe asthma compared with milder disease. To accomplish these goals, subjects with asthma of all levels of disease severity were recruited and underwent a comprehensive characterization to identify clinical phenotypes through which severe asthma might be defined.¹² To explore and define the pathobiology of severe asthma in these well characterized patients, it was necessary to obtain samples from the airways to describe patterns of inflammation and what processes may be dysregulated in severe asthma. Although many subjects underwent sputum induction for evaluation of airway inflammatory cells and soluble mediators,¹³ this procedure preferentially samples the large proximal airways and does not allow assessment of inflammation more peripherally or unique features of airways remodeling. To explore

differences in submucosal inflammation and architectural changes in the airway, investigative bronchoscopy was incorporated as a key component of the SARP.

Because subjects with increasingly severe asthma would undergo bronchoscopy, a subcommittee of investigators was appointed to develop common procedures for study and to maximize safety of subjects. The bronchoscopy section of the SARP Manual of Procedures (MoP) provides a detailed uniform approach to preprocedure assessment of underlying severity of asthma; ongoing evaluation for disease stability before, during, and after bronchoscopy; and consistent postprocedure follow-up to assess the occurrence of adverse effects. The aim of this study was to evaluate prospectively changes in pulmonary function and the frequency of respiratory-related events, including hospital-based health care utilization (HCU) and need for oral corticosteroids in subjects with not severe and severe asthma undergoing investigative bronchoscopy in SARP.

METHODS

SARP

After establishing standard operating procedures, including a review by an independent data safety monitoring board (DSMB) and approval by the institutional review boards at each site, subjects underwent a comprehensive phenotypic characterization as previously described.¹² Briefly, after subjects provided written informed consent, clinical staff administered questionnaires (asthma symptoms, medication use, medical history, and HCU), performed allergen skin prick testing, and performed a comprehensive pulmonary function evaluation on several days including baseline prebronchodilator spirometry, response to short-acting β -agonists (2-8 puffs albuterol), and methacholine challenge. After review of clinical data by investigators, a subset of subjects with severe and not severe asthma and normal healthy subjects were recruited for investigative bronchoscopy studies (see inclusion criteria in Table I).

Bronchoscopy MoP

Before initiation of bronchoscopy studies, a subcommittee of investigators was appointed to develop a MoP for investigative bronchoscopy. An independent DSMB reviewed the MoP with ongoing oversight by this committee through review of clinical site experience and adverse events. The institutional review board at each clinical site also reviewed and approved the bronchoscopy MoP. The entire bronchoscopy MoP is provided as an attachment in an online data supplement (see this article's Table E1 in the Online Repository at www.jacionline.org for table of contents of MoP). Clinical sites were required to complete several phases wherein investigators requested permission to perform bronchoscopy on subjects with increasingly severe airflow obstruction using a stepwise algorithm. A subset of the severe asthma group was defined *a priori* as having very severe asthma (VSA) on the basis of baseline severe airflow obstruction ($FEV_1 < 60\%$ predicted after bronchodilators), a therapeutic requirement of chronic oral corticosteroids, and recent or intensive HCU in the past year (see criteria in Table II). Individual centers were required to demonstrate bronchoscopy experience with subjects with severe asthma before progressing to VSA, and their request was reviewed and approved by the bronchoscopy subcommittee before being sent to the DSMB for further review. Only after the formal approval by the DSMB did any site proceed to the next level of asthma severity.

Bronchoscopy procedures

All subjects received albuterol before the bronchoscopy, and spirometry was performed before (prealbuterol $FEV_1\%$ predicted) and after (postalbuterol $FEV_1\%$ predicted) administration. Each center was then allowed to follow its standard operating procedures and institutional rules with regard to conscious sedation (choice of drug and route of administration), local anesthesia (nebulized, atomized, or topical lidocaine), and the use of supplemental

TABLE I. Inclusion criteria for SARP bronchoscopy subjects

All subjects
Age ≥ 18 y and ≤ 60 y*
Nonsmoking (< 5 pack-year tobacco exposure)
No history of coexisting lung disease
No uncontrolled comorbidities
Able to provide written informed consent
Normal healthy controls
No history of asthma or respiratory symptoms
Normal pulmonary function tests ($FEV_1 > 75\%$ predicted; $FEV_1/FVC > 70\%$)
Negative methacholine bronchoprovocation ($PC_{20} \geq 25$ mg/mL)
All subjects with asthma
Clinical history consistent with asthma
Meet ATS criteria for diagnosis of asthma ¹⁴ with EITHER/OR
• Bronchodilator response to albuterol ($\geq 12\%$ change in FEV_1)
• Positive methacholine bronchoprovocation ($PC_{20} < 25$ mg/mL)†
Clinically stable asthma as determined by the bronchoscopist
Subjects with not severe asthma
Treatment with no or low-dose inhaled corticosteroids
Subjects with severe asthma
Meet ATS workshop criteria for the definition of severe/refractory asthma ¹⁵ with
1 major characteristic
• Treatment with oral corticosteroids (≥ 20 mg/d) for $\geq 50\%$ of year AND/OR
• Treatment with high-dose inhaled corticosteroids‡
AND AT LEAST 2 minor characteristics
• Treatment with additional daily second controller medication
• Short-acting β -agonist use on a daily or near-daily basis
• Persistent airway obstruction ($FEV_1 < 80\%$ predicted)
• One or more urgent care visits for asthma per year
• Three or more oral steroid bursts per year
• Prompt deterioration with $\leq 25\%$ reduction in corticosteroid dose
• Near-fatal asthma event in the past

FVC, Forced vital capacity.

*Upper age limit imposed based on concerns for increasing incidence of significant comorbidities (such as heart disease, diabetes, hypertension, renal failure) in subjects > 60 years of age. Investigators were allowed to request approval for older subjects from the steering committee after review of medical records.

†Subjects with $FEV_1 < 55\%$ predicted did not undergo methacholine bronchoprovocation.

‡High-dose inhaled corticosteroid defined as a dose equivalent to ≥ 880 μ g fluticasone propionate.

oxygen. Bronchoscopic procedures were performed in accordance with the specific aims of the investigative site and could include bronchoalveolar lavage (BAL), endobronchial brushing, mucosal biopsy, and, at 1 site, trans-bronchial biopsies. The investigator determined the order of procedures and choice of forceps at each clinical site. Initial BAL was performed with 100 mL prewarmed saline with aspiration of BAL fluid by hand suction for shared samples, but investigators were permitted to instill additional volume at their discretion. Subjects who underwent transbronchial biopsies did not have BAL. After the removal of the bronchoscope, healthy controls and subjects with not severe asthma were observed for at least 1 hour postprocedure and were eligible for discharge when their FEV_1 on postbronchoscopy spirometry returned to within 85% of the initial FEV_1 before bronchoscopy. Subjects who failed to achieve this benchmark or who required more than 3 albuterol treatments post-procedure were admitted to the hospital for overnight observation. Subjects with severe asthma and VSA underwent spirometry before transfer to a hospital setting for scheduled precautionary overnight observation. These subjects were discharged in the morning after assessment of asthma stability by the investigator. The percent change in $FEV_1\%$ predicted was calculated as the difference in $FEV_1\%$ predicted from prebronchodilator spirometry (before

TABLE II. Identification of subjects with VSA for in-hospital overnight observation

Subjects with VSA meet any 1 of the following criteria:
• Treatment with chronic oral corticosteroid ≥ 20 mg prednisone daily
• Evidence for worsening asthma control/clinical instability in the past 2 wk manifest by any 1 of the following*:
– Increase in short-acting β -agonist use (≥ 8 puffs over baseline in past 48 h)
– Change in oral corticosteroid dose or escalation of inhaler therapy
– Exacerbation of asthma requiring corticosteroids and/or physician evaluation
• Evidence for chronic clinical asthma instability
– ≥ 6 Asthma exacerbations in past 180 d
• Recent hospital-based HCU
– Hospitalization for asthma within the past 6 mo†
– Endotracheal intubation for asthma symptoms within the past 1 y‡
• Severe airflow obstruction with postbronchodilator $FEV_1 < 60\%$ predicted

Bronchoscopy was postponed for *14 days if any of these criteria were present, †at least 6 weeks after a hospitalization for asthma, and ‡more than 6 months after endotracheal intubation.

albuterol and bronchoscopy) and the lowest FEV_1 recorded by spirometry in the hours after bronchoscopy was performed.

Surveillance for adverse events

Study coordinators contacted subjects by telephone for 3 days after bronchoscopy and administered a standardized questionnaire to ascertain the frequency of fever, cough, chest pain, shortness of breath, and hemoptysis. Subjects were asked to return to the clinical site for further evaluation whenever needed. Investigators prescribed oral corticosteroids or antibiotics at their discretion. Subjects who went to the emergency department (ED) or required an unscheduled or extension of a planned hospitalization (> 24 hours) for asthma exacerbation or asthma-related symptoms were reported to the DSMB within 24 hours of the investigator becoming aware of the event.

Statistical analysis

Results are presented as percentages or means (SDs). Continuous variables were compared among groups using ANOVA models, categorical variables using χ^2 tests for association. Analyses were carried out both among the 4 groups (normal and 3 asthma groups) and among the 3 asthma groups only. Comparisons of the frequency of cough, chest pain, and shortness of breath postbronchoscopy were adjusted for frequency of reported baseline symptoms before the procedure by using logistic regression models. Associations between continuous variables are summarized by using the Spearman rank correlation coefficient. A P value $< .05$ was considered statistically significant for these comparisons.

A multivariate model was constructed to identify potential predictors of the change in percent predicted FEV_1 postprocedure. Thirty-three covariates were initially selected for this analysis, including clinical center, subject data (age, sex, race, HCU, medication use, disease severity), physiologic measures (lung function, PC_{20} , skin test positivity), inflammatory markers (IgE, blood eosinophils, exhaled nitric oxide, BAL cell counts), and procedural variables from bronchoscopy (procedures performed, medications used, BAL recovery, procedure time). To account for missing data, a multiple imputation approach was used to produce 10 simulated datasets and perform model selections. Fourteen covariates were chosen by more than 2 models (baseline $FEV_1\%$ predicted, $FEV_1\%$ reversibility, BAL performed, brushing performed, fentanyl given, procedure time, BAL percent recovery, PC_{20} , exhaled nitric oxide, number of positive skin tests, BAL eosinophils, age, body mass index [BMI], race) and were included in the final covariate list, which was then applied to each dataset. These models were combined to get estimates of effect size of a given covariate on change in FEV_1 after bronchoscopy. A P value $< .05$ was considered statistically significant.

TABLE III. Clinical characteristics of subjects

	Normal n = 97	Not severe n = 196	Severe n = 102	Very severe n = 41	P value all	P value asthma only [‡]
Age at enrollment (y)	31 (10)	34 (11)	39 (12)	43 (11)	<.0001	<.0001
Sex (% female)	60	63	61	59	.94	.86
Race (% white)	73	71	65	71	.57	.48
BMI	27 (7)	28 (7)	30 (6)	30 (6)	.009	.04
Percent with BMI >30	26	26	47	53	<.0001	<.0001
Baseline lung function*						
FEV ₁ % predicted	100 (11)	88 (15)	73 (16)	55 (21)	<.0001	<.0001
FVC% predicted	102 (11)	96 (13)	85 (17)	74 (17)	<.0001	<.0001
FEV ₁ /FVC (%)	0.82 (0.1)	0.75 (0.1)	0.67 (0.1)	0.56 (0.1)	<.0001	<.0001
Methacholine challenge (n)	97	190	68	4		
PC ₂₀ (mg/mL) [†]	49.0 (0.03)	1.51 (0.67)	0.72 (0.68)	0.56 (0.82)	<.0001	.003
Subjects with ≥1 positive skin prick test (%)	39	85	76	68	<.0001	.03
Asthma medications (% subjects)						
Inhaled corticosteroids		60	99	90		<.0001
Long-acting β-agonists		43	90	83		<.0001
Oral corticosteroids		1	21	80		<.0001
HCU for asthma (% subjects)						
ED, past year		11	40	78		<.0001
Hospitalization, past year		1	20	59		<.0001
Intensive care unit, ever		9	35	51		<.0001

FVC, Forced vital capacity.

Numeric data presented as mean (SD) or [†]geometric mean (log₁₀ SD).

*Prebronchodilator spirometry measurements after an appropriate medication withhold.

[‡]Three-way comparison of asthma groups only.

RESULTS

Characteristics of subjects enrolled in bronchoscopy procedures

Between May 2003 and September 2009, 436 subjects underwent investigative bronchoscopy at 9 clinical sites as part of the SARP (see this article's [Table E2](#) in the Online Repository at www.jacionline.org). In general, the demographics of this subset of subjects with asthma ([Table III](#)) reflect those of the entire SARP cohort as previously reported.¹² Subjects with asthma in the bronchoscopy cohort were divided into 3 groups for the purposes of this safety analysis: not severe asthma, severe asthma, and VSA, with VSA as defined *a priori* on the basis of baseline airflow obstruction, medication requirements, and recent frequent HCU ([Table II](#)). Compared with bronchoscopy subjects with severe asthma, individuals in the not severe group were younger, had a lower BMI, and had higher baseline lung function (mean FEV₁, 88 ± 15% predicted). The not severe asthma group was treated with diverse medication regimens but as a group had few reported asthma exacerbations and overall lower HCU during the previous 12-month period. In contrast, subjects in the severe asthma group were older, nearly half were obese with a BMI >30 kg/m², and they reported higher recent HCU and had lower pulmonary function (mean FEV₁, 73 ± 16% predicted) despite treatment with high doses of inhaled corticosteroids and long-acting β-agonists. The VSA group had the lowest mean FEV₁ (55 ± 21% predicted) and the greatest frequency of recent HCU despite the requirement for treatment with chronic oral corticosteroids (>20 mg prednisone daily) in 80% of these subjects.

Bronchoscopy procedures

Medication use and procedural details are shown in [Table IV](#). FEV₁ measurements preprocedure were highly correlated with baseline FEV₁% predicted previously measured during the study

($r = 0.86$; $P < .0001$), indicating stable lung function at the time of bronchoscopy. Benzodiazepines were the most common sedative used in all groups (midazolam, median dose, 4 mg; interquartile range, 2–6 mg). Midazolam doses increased with procedure time ($r = 0.39$; $P < .0001$), and both were highest in the VSA group ($P < .0001$). Opiates, specifically fentanyl and alfentanil, were used more commonly in the severe groups ($P < .0001$). Topical lidocaine doses were greatest in the VSA group, and this correlated weakly with procedure time ($r = 0.10$; $P = .04$). Fewer subjects with VSA underwent bronchoalveolar lavage (73% vs 89% to 97%; $P = .003$), and BAL recovery was lowest in this group ($P < .0001$). All 3 procedures (BAL, endobronchial brushings, and biopsies) were performed in the majority of subjects (72%). Forty-six subjects with asthma underwent transbronchial biopsies at 1 site; BAL was not performed in these subjects.

HCU after investigative bronchoscopy

A total of 9 subjects were evaluated or monitored in hospital settings after bronchoscopy ([Table V](#)). All but 1 had severe asthma or VSA. Three subjects developed worsening of asthma during their protocol mandated overnight in-hospital observation period (subjects 1–3). These subjects remained in the hospital for additional intravenous or oral corticosteroids and continued inpatient observation at the discretion of the investigator (2–4 days). One subject with severe asthma who was not scheduled for overnight observation failed to recover lung function to 85% of preprocedural values (FEV₁, 79% predicted preprocedure decreased to 57% predicted postprocedure) and, according to SARP protocol, was observed overnight before being discharged on oral corticosteroids the next morning (subject 4). One subject went to the ED for an exacerbation of her asthma several days after bronchoscopy had been attempted but was unsuccessful because of inability to pass the vocal cords. She was treated with oral

TABLE IV. Procedural details during bronchoscopy

	Normal n = 97	Not severe n = 196	Severe n = 102	Very severe n = 41	P value all	P value asthma only†
% Predicted FEV ₁ prealbuterol	99 (12)	90 (15)	75 (18)	58 (21)	<.0001	<.0001
% Predicted FEV ₁ postalbuterol	102 (13)	96 (14)	81 (16)	68 (21)	<.0001	<.0001
Sedative use (% subjects)*						
Midazolam	95	93	97	100	.18	.08
Fentanyl/alfentanil	44	58	81	90	<.0001	<.0001
Scope time (min)	24 (10)	24 (10)	27 (11)	32 (8)	<.0001	<.0001
Total lidocaine used (mg)	355 (194)	347 (151)	312 (165)	425 (117)	.003	.0005
Procedures done (% subjects)						
BAL	97	89	92	73	.003	.005
BAL % recovery	60 (14)	55 (14)	49 (15)	36 (17)	<.0001	<.0001
Bronchial brushings (%)	79	79	72	83	.35	.21
Endobronchial biopsies (%)	95	93	98	98	.30	.16
Transbronchial biopsies, n	0	22	11	13		
% Subjects with 3 procedures‡	76	71	69	66	.28	.70

Numeric data presented as mean (SD).

*The most common sedatives used are listed. Alternative sedatives used less commonly included meperidine (10% subjects) and morphine (8% subjects).

†Three-way comparison of asthma groups only.

‡Subjects who had transbronchial biopsies did not undergo BAL.

corticosteroids then discharged from the ED (subject 5). There was no long-term loss of asthma control in any of these subjects. Of the remaining 4 subjects who went to the ED after bronchoscopy, 2 reported pleuritic chest pain (subjects 6 and 7), 1 complained of a rash (subject 8) and 1 subject was experiencing a panic attack (subject 9). None of these subjects developed an asthma exacerbation.

Changes in FEV₁ after bronchoscopy among subject groups

A comparison of the postbronchoscopy percent change in percent predicted FEV₁ among the subject groups showed no statistically significant difference in the distribution of percent fall in FEV₁ ($P = .30$; Fig 1). In the asthma groups, half of the subjects had a $\leq 5\%$ fall in FEV₁, and there was no difference between the not severe and severe asthma subgroups. All subjects with not severe asthma had improvement in their FEV₁ to 85% of the preprocedure value either spontaneously over time or after bronchodilator treatment and were discharged 1 to 2 hours after bronchoscopy, including those whose FEV₁ decreased more than 20% ($n = 24$). Although precautionary overnight observation was mandated by the SARP protocol for subjects with VSA, it was also recommended for subjects in the severe asthma group, and investigators chose to observe most subjects in this group overnight also (75% subjects). Ninety-seven percent of the subjects scheduled for overnight observation were discharged the following morning, including 22 of the 24 subjects with severe asthma who had a $>20\%$ decrease in FEV₁% predicted on the day of the procedure.

Effect of baseline lung function on change in FEV₁

A correlation of baseline pulmonary function measures (on a different day from bronchoscopy) with percent change in FEV₁ after bronchoscopy revealed weak relationships between baseline percent predicted FEV₁ (with withholding of β -agonists; $r = -0.13$; $P = .02$) and reversibility after 6 to 8 puffs of albuterol ($r = 0.20$; $P = .0003$). Thus, subjects with asthma with higher baseline FEV₁ had greater decreases in FEV₁ after bronchoscopy,

and those with greater reversibility had smaller decreases in FEV₁ after the procedure. There was no relationship between PC₂₀ and percent change in FEV₁ after bronchoscopy ($r = -0.01$; $P = .91$), although subjects with an FEV₁ $<55\%$ predicted did not undergo methacholine challenge and thus are not included in this analysis (33% of the severe and 90% of the VSA groups). On the day of the bronchoscopy, an inverse relationship between preprocedure prealbuterol percent predicted FEV₁ and the change in FEV₁ after bronchoscopy was still observed ($r = -0.21$; $P < .0001$; Fig 2), with larger decreases in FEV₁ observed in those subjects with better lung function. After administration of albuterol before bronchoscopy, however, there was an improvement in FEV₁% predicted in most subjects, and the relationship between FEV₁ and percent change in FEV₁ was no longer present ($r = -0.08$; $P = .18$). The change in FEV₁ for the 9 subjects who were evaluated or monitored in hospital settings after bronchoscopy is shown in Fig 2 (closed triangles and circles).

In a multivariate analysis to identify predictors of change in FEV₁, baseline FEV₁% predicted was the most statistically significant predictor of a change in FEV₁ after bronchoscopy, with a -3.6% (95% CI, -4.7% , -2.5%) decrease in FEV₁% predicted for every 10% increase in baseline FEV₁ ($P < .0001$). The strongest other predictors in this analysis were covariates related to BAL, with an effect of -11.6% (95% CI, -19.4% , -3.8%) decrease in postprocedure FEV₁ if BAL was performed ($P = .003$) and a -1.6% (95% CI, -2.9% , -0.3%) decrease in FEV₁ for every 10% less BAL recovered ($P = .02$).

Symptoms after bronchoscopy

In the 3 days after bronchoscopy, the most commonly reported symptoms in the not severe asthma, severe asthma, and VSA groups were cough (50%, 47%, and 78% of subjects, respectively), shortness of breath (14%, 23%, and 53%), chest pain (11%, 17%, and 35%), and blood-streaked sputum (17%, 23%, and 38%; Table VI). Although these symptoms were more frequently reported in the VSA group, only cough and blood-streaked sputum were statistically significantly different among the groups after the frequency of baseline symptoms was used

TABLE V. Subjects with HCU after bronchoscopy

Subject no.	Age (y)/ race/sex	Asthma severity	Baseline clinical data			Day of bronchoscopy		Description of event and treatment given
			Chronic OCS	ED in past y	Baseline FEV ₁ * (%)	Pre bronch FEV ₁ *	Scheduled overnight?	
1	38 BF	Severe	N	Y	60	82	Y	Continued hospitalization for 4 days for asthma exacerbation; treated with IV CS and OCS, antibiotics On review of event, patient had asthma exacerbation 6 wk before procedure and remote breast cancer with chest irradiation (but normal current CXR)
2	58 WF	Severe	Y	Y	63	54	Y	Continued hospitalization for 1 extra day for asthma exacerbation; treated with OCS, antibiotics
3	42 BF	VSA	Y	Y	59	52	Y	Continued hospitalization for 1 extra day for asthma exacerbation, chest pain; treated with IV CS and OCS
4	18 BF	Severe	N	Y	81	79	N	Unplanned hospitalization for failure to meet FEV ₁ discharge criteria; treated with OCS On review of event, patient had asthma exacerbation 12 wk before procedure
5	22 WF	VSA	Y	Y	40	44	N	Bronchoscopy was not completed because of inability to pass vocal cords ED visit 3 d after bronchoscopy for asthma exacerbation with syncope; CTA showed no PE; treated with OCS, antibiotics
6	35 WF	VSA	Y	Y	37	36	Y	Discharged in stable condition after overnight stay Returned to ED that evening with pleuritic chest pain; treated with analgesics only
7	24 BM	Severe	N	Y	41	46	N	ED visit (then hospitalization) 6 d after bronchoscopy for chest pain; CT showed pneumatocele in area where transbronchial biopsies were done, supportive care only
8	49 BF	VSA	Y	Y	35	48	Y	Discharged in stable condition after overnight stay Returned to ED 2 d after bronchoscopy for lower extremity rash; treated with OCS, antihistamines for allergic reaction; not clearly related to procedure
9	43 BF	Not severe	N	N	92	93	N	ED visit 3 d after bronchoscopy for sudden shortness of breath caused by panic attack; no treatment given; not related to procedure.

B, Black; CT, chest CT; CTA, chest CT with angiogram (pulmonary embolism protocol); CXR, chest radiograph; IV CS, intravenous corticosteroids; N, no; OCS, oral corticosteroid; PE, pulmonary embolism; W, white; Y, yes.

*FEV₁ presented as percent predicted FEV₁. Baseline FEV₁ is measured with appropriate medication withheld on a different day. Prebronch FEV₁ is the FEV₁ measured prior to preprocedure administration of albuterol (before bronchoscopy).

as a covariate ($P = .002$ and $P = .02$, respectively). Fever was infrequently reported (2% to 11%) and was similar in the 4 groups ($P = .06$).

Treatments after bronchoscopy

Oral corticosteroids were prescribed more frequently in the postprocedure period in the severe asthma (25%) and VSA groups (63%) compared with the not severe group (4%; $P < .001$; Table VI). Specifically, subjects with severe asthma with the greatest baseline airflow obstruction (FEV₁ < 60% predicted) and those who reported an ED visit in the past year were more likely to be treated with systemic corticosteroids after bronchoscopy (both $P < .0001$). Antibiotics were prescribed in only 7 subjects, but all were in the severe asthma and VSA groups ($P = .003$), and all of them had reported an ED visit in the past year ($P = .002$). All 5 subjects who had an asthma exacerbation after bronchoscopy also reported an ED visit within the past 12 months (100% vs 48%; $P = .03$) and a previous history of pneumonia (100% vs 54%; $P = .05$) compared with the subjects with severe asthma

who did not require additional evaluation and treatment postprocedure. There were no differences in bronchoscopic techniques or procedures between the subjects with severe asthma who did or did not develop exacerbations, nor those who did or did not receive oral corticosteroids or antibiotics after bronchoscopy.

DISCUSSION

The current study reports our experience with investigative bronchoscopy in a large subset of subjects from the SARP, including 143 subjects with severe asthma who met the American Thoracic Society (ATS) workshop definition of severe asthma, 196 subjects with not severe asthma, and 97 normal controls. The aim of our study was to evaluate prospectively changes in pulmonary function and the frequency of respiratory-related events in subjects with not severe and severe asthma undergoing investigative bronchoscopy in SARP. Our results support the safety of investigative bronchoscopy in subjects with severe asthma and extend previous reports of the safety of this procedure in subjects with mild to moderate disease.⁶⁻¹¹

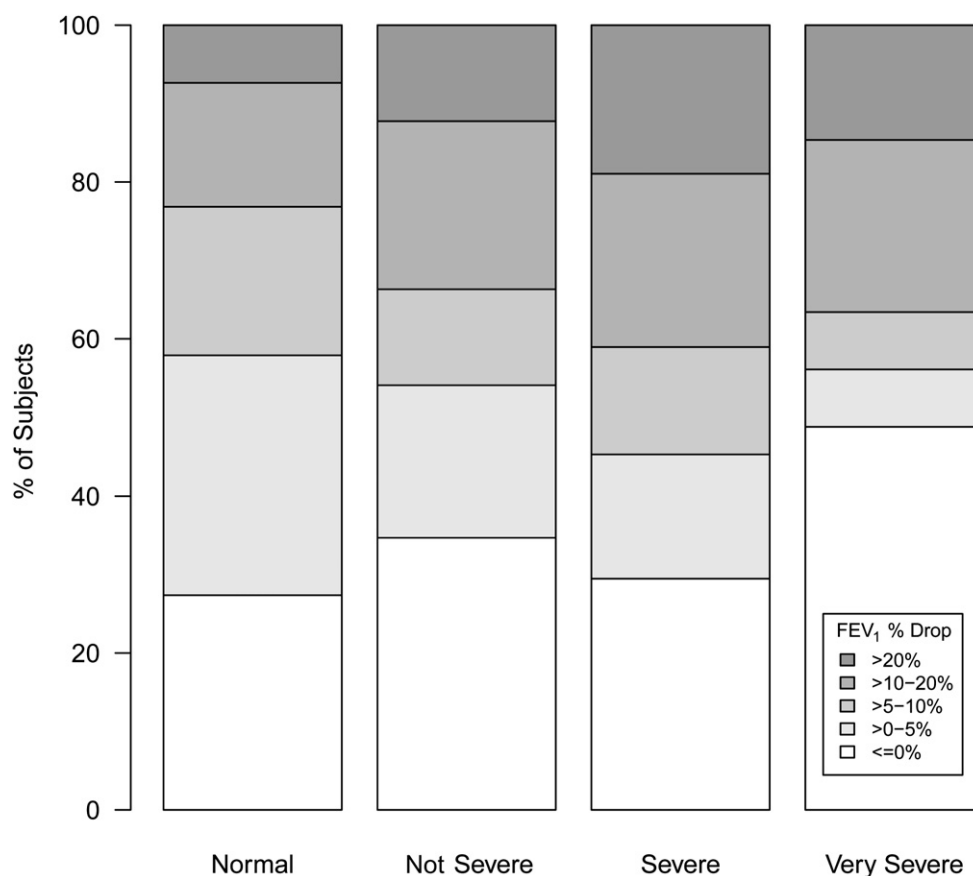


FIG 1. Change in FEV₁ after bronchoscopy in the 4 groups of subjects. Shown is the percent change in percent predicted FEV₁ from the first FEV₁ before albuterol administration to the lowest FEV₁ after bronchoscopy. There was no statistically significant difference in the distribution of percent change in percent predicted FEV₁ among the groups ($P = .30$).

Investigative bronchoscopy was well tolerated by subjects with severe asthma and VSA, with only 5 asthma exacerbations experienced (<1.5% of the asthma subjects), which resolved quickly (2-4 days). Identification of clinical markers that might have predicted loss of asthma control after bronchoscopy was difficult because of the scarcity of these events. Although all 5 of the subjects who had asthma exacerbations after bronchoscopy had severe airflow obstruction at baseline (FEV₁ 40% to 63% predicted), reported an ED visit in the past year, and had a previous episode of pneumonia, these clinical characteristics were common in the severe asthma groups in general and not specific to these subjects. Likewise, although a >20% decrease in FEV₁ was observed in 3 of these 5 subjects, there were 21 other subjects with severe asthma who sustained similar falls in their FEV₁ but were discharged the following morning after planned precautionary overnight observation. Importantly, of the 5 subjects who had asthma exacerbations, 4 were being observed in a hospital setting according to SARP protocol, and none of these required a higher level of care than a traditional inpatient medical bed. All of these events occurred early in the SARP program and may have resulted from more cautious care of worsening asthma in this research setting. The only asthma exacerbation resulting in an ED visit occurred in a subject with a history of many previous and recent ED visits and in whom the bronchoscope never passed the vocal cords.

Although subjects with severe asthma had lower baseline lung function, there was a <10% decrease in percent predicted FEV₁

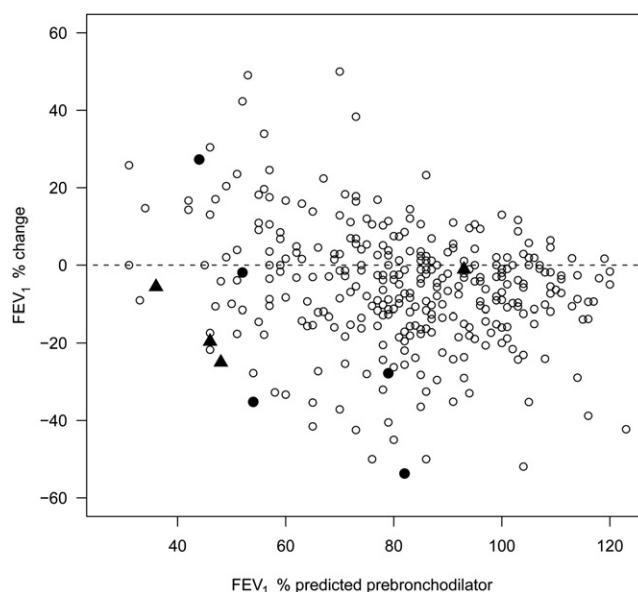


FIG 2. Change in FEV₁ after bronchoscopy for individual subjects. There is a mild relationship ($r = -0.21$; $P < .0001$) between better baseline lung function and greater percent decrease in FEV₁. The *closed circles* represent the subjects who had asthma exacerbations. The *closed triangles* are subjects who went to the ED with other complaints.

TABLE VI. Symptoms and treatments 1 to 3 days after bronchoscopy

	Normal n = 97	Not severe n = 196	Severe n = 102	Very severe n = 41	P value all	P value† asthma only
Cough*	54	50	47	78	.002	.01
Chest pain*	2	11	17	35	.15	.12
Shortness of breath*	3	14	23	53	.14	.07
Blood-streaked sputum	15	17	23	38	.02	.02
Nausea	6	4	7	8	.53	.35
Fever	7	4	11	2	.06	.02
Medications used						
postprocedure (% subjects)						
Antipyretic	15	12	23	20	.12	.06
Antibiotic	0	0	4	8	.0007	.003
Prednisone	0	4	25	63		<.0001

Data presented as percentage of subjects.

*P value adjusted for baseline symptom frequency reported on clinical characterization questionnaire.

†Three-way comparison of asthma groups only.

observed after bronchoscopy in the majority of these subjects, similar to that seen in the not severe asthma and normal control groups. This finding is in agreement with a smaller previous study by Van Vyve et al,⁸ in which there were 10 subjects with a preprocedure FEV₁ <60% predicted and an elevated severity score but no observed difference in percent change in FEV₁ despite the severity of their asthma.

Subjects with lower baseline lung function (FEV₁% predicted) had smaller (not larger) decreases in FEV₁ after bronchoscopy. Likewise, subjects with greater baseline reversibility to short-acting β -agonists (6-8 puffs) were less likely to sustain large decreases in FEV₁ after the procedure even when adjusting for baseline percent predicted FEV₁. Taken together, these associations suggest that subjects with severe airflow obstruction, many of whom respond well to bronchodilator administration,¹² are not at greater risk for large falls in FEV₁ after bronchoscopy. This may be partially a result of the protocol-required pretreatment of all SARP subjects with albuterol with subsequent improvement in FEV₁ before to bronchoscopy.

Conversely, some subjects with asthma with preserved lung function (and thus mathematically less reversibility) had large decreases in their FEV₁% predicted after bronchoscopy. At least 2 studies have reported an inverse relationship between the degree of baseline airway hyperresponsiveness (PC₂₀ methacholine) and percent change in FEV₁ or peak expiratory flow rates after bronchoscopy, suggesting that the presence of greater bronchial hyperresponsiveness might lead to exaggerated changes in FEV₁ with airway instrumentation in subjects with preserved baseline lung function.^{6,9} A similar analysis of our subjects with a baseline FEV₁% predicted >55% who underwent methacholine challenge, however, did not show any association between the level of bronchial hyperresponsiveness and the decrease in FEV₁ after bronchoscopy.

Of the 33 covariates used in the multivariate analysis, the only statistically significant procedural predictor of a greater fall in FEV₁ after bronchoscopy was the performance of a BAL. Furthermore, there was an additional, although smaller magnitude, effect seen with lower BAL fluid recovery. Although these results should be interpreted with care given the need to impute data for the subjects who did not have BAL performed, these findings do suggest that investigators should be cautious when performing BAL in subjects with asthma, especially if initial fluid recovery is modest.

Cough was the most frequently reported symptom after bronchoscopy, especially in the severe asthma groups. These groups were more likely to receive oral corticosteroids after the procedure, perhaps because of complaints of persistent cough. Likewise, subjects who reported a recent ED visit or who had a baseline FEV₁ <60% predicted were more frequently treated with oral corticosteroids regardless of a minimal change in FEV₁ after bronchoscopy. Because investigators had the discretion to treat subjects after bronchoscopy on the basis of their clinical judgment, this finding suggests that they preferred to treat this group of patients with severe asthma on the basis of their baseline clinical data, not events surrounding the bronchoscopic procedure.

There are some limitations to this study. First, despite the commitment and effort to a common bronchoscopy MoP to monitor pulmonary function and respiratory-related events, the nature of the SARP network (8 independent investigator-initiated grants) required flexibility of the actual bronchoscopy procedures to allow investigators to meet the specific aims of their independent grants. Second, the goal of some sites was to study the most severe patients, whereas others focused on a broader range of disease severity. Thus, inherent variability among the sites confounds interpretation of some of the data and may impact our ability to generalize our findings to other investigators. Finally, the low incidence of adverse events in SARP may be a best case scenario that reflects the years of experience of many of our investigators.

The current study used a standardized approach to investigative bronchoscopy in a large cohort of subjects with severe and not severe asthma to examine prospectively changes in lung function and respiratory-related events associated with this research procedure. We confirmed previous reports describing safety aspects of investigative bronchoscopy in patients with mild to moderate asthma, but more importantly, our results support the safety of this procedure in subjects with severe asthma. Despite severe airflow obstruction, complex medication regimens and recent high HCU in the severe asthma groups, there were very few asthma exacerbations after the procedure and, when they occurred, they typically resolved within days after the bronchoscopy. Our results confirm that bronchoscopy with appropriate precautions is well tolerated in patients with mild-moderate as well as severe asthma and can continue to be a valuable investigative procedure to define airway inflammation in asthma.

We thank all of the subjects who agreed to participate in the bronchoscopy portion of SARP as well as the physicians, bronchoscopy technicians, nurses, and coordinators who ensured their safety during the procedure.

Clinical implications: Investigative bronchoscopy has been used to study pathobiologic changes in milder asthma. Our experience confirms that this procedure can be safely performed in subjects with severe asthma.

REFERENCES

1. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy Clin Immunol* 2007;120(suppl 5):S94-138.
2. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143-78.
3. National Institutes of Health workshop summary: summary and recommendations of a workshop on the investigative use of fiberoptic bronchoscopy and bronchoalveolar lavage in individuals with asthma. *J Allergy Clin Immunol* 1985;76(pt 1):145-7.
4. Workshop summary and guidelines: investigative use of bronchoscopy, lavage, and bronchial biopsies in asthma and other airway diseases. *J Allergy Clin Immunol* 1991;88:808-14.
5. Busse WW, Wanner A, Adams K, Reynolds HY, Castro M, Chowdhury B, et al. Investigative bronchoprovocation and bronchoscopy in airway diseases. *Am J Respir Crit Care Med* 2005;172:807-16.
6. Djukanovic R, Wilson JW, Lai CK, Holgate ST, Howarth PH. The safety aspects of fiberoptic bronchoscopy, bronchoalveolar lavage, and endobronchial biopsy in asthma. *Am Rev Respir Dis* 1991;143:772-7.
7. Chetta A, Foresi A, Bertorelli G, Pesci A, Olivieri D. Lung function and bronchial responsiveness after bronchoalveolar lavage and bronchial biopsy performed without premedication in stable asthmatic subjects. *Chest* 1992;101:1563-8.
8. Van Vyve T, Chanez P, Bousquet J, Lacoste JY, Michel FB, Godard P. Safety of bronchoalveolar lavage and bronchial biopsies in patients with asthma of variable severity. *Am Rev Respir Dis* 1992;146:116-21.
9. Humbert M, Robinson DS, Assoufi B, Kay AB, Durham SR. Safety of fiberoptic bronchoscopy in asthmatic and control subjects and effect on asthma control over two weeks. *Thorax* 1996;51:664-9.
10. Elston WJ, Whittaker AJ, Khan LN, Flood-Page P, Ramsay C, Jeffery PK, et al. Safety of research bronchoscopy, biopsy and bronchoalveolar lavage in asthma. *Eur Respir J* 2004;24:375-7.
11. Julius P, Lommatzsch M, Kuepper M, Bratke K, Faehndrich S, Luttmann W, et al. Safety of segmental allergen challenge in human allergic asthma. *J Allergy Clin Immunol* 2008;121:712-7.
12. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol* 2007;119:405-13.
13. Hastie AT, Moore WC, Meyers DA, Vestal PL, Li H, Peters SP, et al. Analyses of asthma severity phenotypes and inflammatory proteins in subjects stratified by sputum granulocytes. *J Allergy Clin Immunol* 2010;125:1028-36.
14. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987;136:225-44.
15. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. *Am J Respir Crit Care Med* 2000;162:2341-51.

SARP MoP for investigative bronchoscopy

The Bronchoscopy Section (9) of the SARP Manual of Operations is provided in its entirety in a separate PDF file. [Table E1](#) provides a brief description of bookmarks to assist your review of this document. Sections 9.3 and 9.4 detail differences in the SARP MoP as it pertains to subjects <18 years of age. Only 1 pediatric subject is included in the current analysis.

Protocol deviations and changes to the MoP

Early in SARP, an interim data analysis revealed that the total lidocaine dose limit (600 mg or 9 mg/kg, whichever is less) was inadvertently exceeded in 22 subjects (12 normal subjects, 6 subjects with not severe asthma, and 4 subjects with severe

asthma). These subjects received total doses of lidocaine that ranged from 620 to 940 mg, largely because of higher doses of atomized lidocaine applied to the upper airway (which was included in the total reported dose). There were no adverse effects related to these higher doses of lidocaine. Subsequent review of topical anesthesia protocols at all sites (which varied with regard to the use of atomized, gargled, or nebulized lidocaine to anesthetize the airways) led to an amendment to the MoP to standardize the reporting of lidocaine doses. After this change to the protocol, all lidocaine doses are reported as the arithmetic total of lidocaine administered by any route, regardless of whether application is primarily above or below the vocal cords. Lidocaine doses in the current article reflect the total dose of lidocaine given to the subjects during preparation and performance of the procedure.

TABLE E1. SARP bronchoscopy MoP

Section	Pages	Brief description	Comments in reference to current article
9.1	103	Adult standards	
9.1.2	103	Subject selection and characterization	5 Subjects with Chronic Obstructive Pulmonary Disease (COPD) underwent bronchoscopy but are not included in this analysis.
9.1.3	105	Inclusion/exclusion criteria	
	107	Definition of VSA	
	108-9	Phase-in criteria	
9.1.4	109-10	General exclusion criteria	
		Criteria to delay bronchoscopy	
9.1.5	111	Medication dose limits	
9.1.6	111-12	Topical anesthesia dose limits	
9.1.7	113	Procedural monitoring	
9.1.8 – 9.1.12	113-15	Bronchoscopy procedures	Procedures for sharing of BAL fluid and endobronchial brushings and biopsies between sites.
9.1.13	116	Postprocedure monitoring	
9.1.14	117	Hospitalization indicators	
9.2	118-21	Safety algorithm	
9.3	121-3	Pediatric standards: 6-11 y of age	Investigative bronchoscopy was not performed in this age group. The MoP details sample collection from diagnostic bronchoscopies performed for clinical purposes.
9.4	123-33	Pediatric standards: 12-17 y of age	Only 1 adolescent had been studied at the time of this analysis. To date, 2 adolescents have undergone investigative bronchoscopy at 1 center (Washington Univ).
9.5	133-7	Stopping rules and DSMB oversight	
9.6	137-42	Transbronchial biopsies	One investigator (Dr Wenzel) performed this procedure.
9.7	142	Approval to proceed with bronchoscopy	

TABLE E2. Distribution of bronchoscopy subjects at centers

Center*	Normal	Not severe asthma	Severe asthma	VSA	Center total
Brigham & Women's Hospital	0	17	12	3	32
Cleveland Clinic	19	17	9	1	46
Imperial College, UK	0	20	20	0	40
National Jewish Health	21	17	11	11	60
University of Pittsburgh	27	15	6	21	69
University of Virginia	3	5	2	0	10
Wake Forest University	0	35	9	0	44
University of Wisconsin	17	57	16	2	92
Washington University	10	13	17	3	43
Subject group totals	97	196	102	41	436

UK, United Kingdom.

*Emory University is a pediatric clinical site that does not perform investigative bronchoscopy.

Section 9

Bronchoscopy Standards

9.1 Adult Standards

9.1.1 Purpose

It is the main goal of the Bronchoscopy Subcommittee to maximize the safety of subjects participating in the SARP. The secondary goal of the Subcommittee is to facilitate the acquisition of airway samples (BAL fluid, BAL cells, bronchial brushings, and bronchial biopsies) that can be shared with other SARP investigators as *shareable samples*. Although it is desirable to procure *shareable samples* for study by other SARP investigators, this objective should not take precedence over the needs of individual investigators to accomplish the scientific goals outlined in their individual grant. The following aspects of invasive bronchoscopic procedures should be adhered to carefully by each investigator when they tailor specific techniques and protocols.

This document presents 2 protocols: severe asthma and very severe asthma. These protocols are presented together to expedite their review and to highlight their differences. Because research in children differs from research in adults, this document omits the *Pediatric Standards*.

9.1.2 Subject Selection and Categorization

Subjects selected for study can fall into one of three disease categories, one of which (asthma) has three subdivisions. As a result, there will be 5 categories of SARP subjects: healthy controls (HC), mild-to-moderate asthma (MMA), severe asthma (SA), very severe asthma (VSA), and chronic obstructive pulmonary disease (COPD). Definitions of HC, MMA, and COPD can vary from site to site. The distinction between MMA and SA can vary also from site to site; in general, however, subjects with MMA exhibit acceptable clinical asthma

control with common asthma controller medications. This section focuses on 1) the distinction between SA and VSA because the VSA group requires additional safety procedures, 2) exclusion criteria that differentiate VSA from exclusion due to asthma severity, and 3) considerations for bronchoscopy in the 5 subject groups. Generally, subjects in HC, MMA, and SA categories can be studied using generally accepted safeguards. Subjects with VSA require additional safeguards and vigilance. Figure 9.1 depicts the relationships among the study groups.

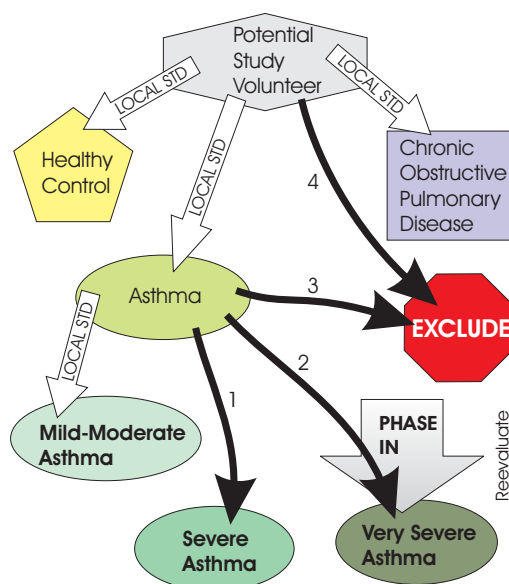


Figure 9.1: There will be 5 groups of SARP volunteers: healthy, chronic obstructive pulmonary disease, mild-to-moderate, severe, and very severe asthma. Because the research questions and control populations will vary, the definitions of healthy, chronic obstructive pulmonary disease, and mild-to-moderate asthma at each center will vary. In contrast, severe asthma has been defined: 1·see INCLUSION CRITERIA FOR ALL ASTHMATIC SUBJECTS (p 106). Very severe asthma has also been defined: 2·see CRITERIA FOR DISTINGUISHING SA FROM VSA (p 107). For subject safety, there are clear exclusion criteria (Section 9.1.4, p 109). These criteria may exclude subjects with more severe asthma depending on their phase-in criteria: 3·see PHASE IN CRITERIA FOR BRONCHOSCOPY IN VERY SEVERE ASTHMA (p 108). A clinically important comorbidity is an exclusion: 4·see EXCLUSION FROM BRONCHOSCOPY FOR AN INDEFINITE PERIOD (p 110). The inclusion of subjects with progressively more severe disease into the very severe asthma group is depicted by the Phase-In arrow; monitoring by the DSMB will occur during the Phase-In period. Local STD, local standards.

An algorithm for caring for subjects who participate as bronchoscopy volunteers has been developed and incorporated into a flow sheet (Section 9.2).

Subjects must meet all inclusion criteria (Section 9.1.3) and must fail to meet all exclusion criteria (Section 9.1.4). Summary tables of inclusion and exclusion criteria are reproduced here.

Table 9.1: General Inclusion Criteria for Asthma Subjects

- Asthma is present, defined by site-specific criteria, and has been classified as MMA, SA, or VSA
- FEV₁ is within acceptable limits (Table 9.3)
- Informed consent is present
- Bronchoscopist has determined that subject is clinically appropriate for bronchoscopy

n.b. This summary provides overview, and is not exhaustive in detail. See Section 9.1.3.

Table 9.2: General Exclusion Criteria for Asthma Subjects

- FEV₁ is less than 35% predicted before, or less than 40% predicted after, bronchodilator administration. This criterion is the most inclusive limit. Additional restrictions may apply. See Table 9.3.
- Asthma is clinically unstable (Section 9.1.4)
- Communication channel is not established for follow-up contacts
- Clinically significant, unstable comorbidities are present

n.b. This summary provides overview, and is not exhaustive in detail. See Section 9.1.4.

Considerations for all subjects

- Ability to cooperate with procedures
- Ability to give consent
- Clotting studies, CBC, and platelet counts may be done as a bronchoscopy screen at the discretion of investigators, but are not required.
- Coexisting lung disease

Considerations for asthmatic subjects

- Clinical stability, consistent with the specific inclusion and exclusion criteria outlined below. A subject judged to be clinically unstable by the investigator or bronchoscopist should generally be excluded from bronchoscopy until acceptable clinical stability, as defined in the inclusion and exclusion criteria (Sections 9.1.3 and 9.1.4), is achieved.
- For participants with severe asthma, or very severe asthma, a competent companion or caretaker should be available at home. Identification of such a person should precede initiation of sedation and bronchoscopy.

- For participants with very severe asthma, additional screening, procedural, monitoring, and follow-up considerations are recommended.

9.1.3 Inclusion Criteria for Asthma (MMA, SA, VSA), COPD, and Healthy Controls

Healthy control (HC) volunteers must meet site-specific requirements for inclusion. Generally, these requirements will include no history of allergies or asthma, normal spirometry, and a trivial or absent smoking history.

Volunteers with chronic obstructive pulmonary disease (COPD) must meet site-specific requirements for inclusion. Generally, these requirements will include a significant tobacco smoking history, and evidence of fixed airflow obstruction. Allergies may or may not be present, but a formal history of asthma is absent.

Volunteers with asthma will meet site-specific criteria, which generally include the demonstration of airflow obstruction which may be reversible with β -agonists. A physician diagnosis of asthma is often present prior to subject enrollment in the SARP. Allergies may or may not be present.

Inclusion Criteria for All Asthmatic Subjects

Subjects must meet each of the following criteria in order to qualify to participate in bronchoscopic study at any level of asthma severity. These criteria, with those of Section 9.1.4, form the border between VSA and Exclude categories in Figure 9.1.

- PFT: prebronchodilator FEV₁ in *Spirometry 1*, obtained prior to bronchodilator administration, must always be $\geq 35\%$ predicted. As detailed in Table 9.3, we will begin with a floor FEV₁ criterion of $\geq 45\%$, prior to bronchodilator, and phase in more severe subjects based on objective evidence of safety and experience, and with monitoring by the Bronchoscopy Subcommittee and the DSMB.
- PFT: postbronchodilator FEV₁ in *Spirometry 2*, obtained after administration of 2.5 mg albuterol by nebulizer, in all cases must be $\geq 40\%$ predicted. As detailed in Table 9.3, we will begin with a floor FEV₁ criterion of $\geq 60\%$, following bronchodilator, and phase in more severe subjects based on objective evidence of safety and experience, and with monitoring by the Bronchoscopy Subcommittee and the DSMB.
- Age: for adult protocols, age of ≥ 18 years and ≤ 60 years. Due to the increasing incidence of comorbidities, and the potential stress of the invasive procedure of bronchoscopy, the age of 60 is selected as conservative and biased in the direction of subject safety. Exceptions to the 60-year limit

may be made on a case-by-case basis, for individuals who demonstrably are free of important comorbidities (see Section 9.4.3, p 110). For those individuals older than 60, an ECG and CXR will have been obtained within the past 6 months. Exceptions for subjects older than > 60 years of age are expected to be uncommon.

- Gender: no selection criteria
- Minority status: no selection criteria
- No hospitalization for asthma within 6 weeks, and no intubation for asthma within 6 months.
- Subject must be judged otherwise to be clinically appropriate for bronchoscopy by bronchoscopist. No specific PFT or other criteria, other than above, are used to document acceptability and appropriateness. Safety of the subject is the overriding concern in making this determination. Details of the clinical course must be detailed in the record.

General Approach to Subject Safety: Rationale for Distinguishing Severe Asthma from Very Severe Asthma

Asthma is temporally variable. Thus, a specific subject may at one time exhibit selection parameters consistent with SA, but at time of bronchoscopy be consistent with VSA. Subjects with VSA may demonstrate considerably greater physiologic brittleness or volatility, and may decompensate acutely with or without warning signs. Thus, the determination of the level of asthma severity, and the consequential procedural and monitoring safeguards which should be employed, must be reassessed on the day of bronchoscopy. Criteria to make this distinction are listed in Section 9.1.3.

Criteria for Distinguishing SA from VSA: VSA/SA Border Criteria

For subjects who otherwise meet criteria for inclusion in the SARP for bronchoscopy, the presence of any of the following characteristics places the subject into the category of Very Severe Asthma, rather than Severe Asthma:

- $FEV_1 < 60\%$ predicted following administration of 2.5 mg albuterol via nebulizer.
- Use of short-acting β -agonists in excess of 8 puffs per day within 48 hours of bronchoscopy
- In the presence of regular long-acting β -agonists, the use of short-acting β -agonists in excess of 4 puff per day within 48 hours of bronchoscopy
- Hospitalization for asthma within 6 months
- Endotracheal intubation for asthma within 1 year

- More than 6 exacerbations in the past 180 days (about one per month)
- Changing dose of oral corticosteroids (up or down) in the past 14 days
- Regular oral corticosteroid dose of 20 mg/day or more
- Asthma exacerbation or other clinical instability in the judgment of the investigator or bronchoscopist
- $D_{L_{CO}}$ may be performed at the discretion of the investigator to clarify the diagnosis if necessary. In this setting, a $D_{L_{CO}}$ of $< 70\%$ predicted will be exclusionary for any asthma group. However, determination of $D_{L_{CO}}$ is not mandatory.

Phase In Criteria for Bronchoscopy in Very Severe Asthma: Exclude/VSA Border Criteria

The SARP investigators place participant safety in first place on our program agenda. Consequently, we will phase in the study of the most severe subjects using conservative criteria initially, with an increasingly inclusive protocol, based on the individual site experience of the SARP investigators, and the oversight of the DSMB.

During the first phase of subject recruitment, all subjects must demonstrate an FEV_1 of at least 45% predicted prior to administration of albuterol, as above, and at least 55% predicted after albuterol. Note that subjects with FEV_1 at least 55% predicted following bronchodilator are generally designated as severe asthma and not very severe asthma. Thus, this phase-in approach effectively eliminates recruitment of VSA subjects until a center has experience in SA. Accrual and experience of asthma subjects will be recorded on a site-by-site (10 SARP sites, 8 SARP centers) basis. The accrual of 7 qualifying subjects at a specific site will constitute *Phase 1*. At the completion of *Phase 1*, the center will ask the Bronchoscopy Subcommittee to review the safety experience in their initial 7 subjects. If approved by the Bronchoscopy Subcommittee, DSMB approval will be sought. On DSMB approval, *Phase 2* will begin. During *Phase 2*, all subjects with VSA must demonstrate an FEV_1 of at least 40% predicted prior to administration of albuterol, as above, and at least 50% predicted after albuterol. These subjects will have more significant airway obstruction, but will still have clinically important β -agonist induced reversibility of the obstruction. After the accrual of 7 subjects meeting this criterion at a specific center, the safety experience will be submitted to the Bronchoscopy Subcommittee and DSMB for review and approval to move to *Phase 3* for the duration of the SARP projects. In *Phase 3*, all subjects with VSA must demonstrate an FEV_1 of at least 35% predicted prior to administration of albuterol, as above, and at

least 40% predicted after albuterol. Safety data from these subjects collected during *Phase 3* will be submitted to the DSMB for review every 10 subjects enrolled at each center. Table 9.3 summarizes these criteria.

Table 9.3: Absolute FEV₁ Criteria for Inclusion in the Very Severe Asthma Category*

	<i>Phase 1, SA</i> 7 Qualifying subjects	<i>Phase 2, VSA</i> 7 Qualifying subjects	<i>Phase 3, VSA</i> Until completion
FEV ₁ prealbuterol	≥ 45% predicted	≥ 40% predicted	≥ 35% predicted
FEV ₁ postalbuterol	≥ 55% predicted	≥ 50% predicted	≥ 40% predicted
Center sample size [†]	7	7	10‡

* To be included in a category, a subject must meet both criteria. Reversibility criteria have no bearing on inclusion.

† To qualify for DSMB review and study of next phase of severity

‡ DSMB safety review after every 10 subjects with very severe asthma

9.1.4 General Exclusion Criteria

- Inability to provide informed consent
- Inability or unwillingness to complete schedule SARP procedures
- Lack of reliable communications channel (hard-wire phone, cell phone, email for follow-up contacts after bronchoscopy)

Exclusion from SARP Enrollment

The following exclusion criterion should exclude asthmatic and normal subjects, but not COPD subjects, from enrollment in SARP: Subjects with current smoking history, or smoking history within one year, are excluded; former smokers with < 5 pack-year total history, who have been abstinent for at least one year may be included at the discretion of the investigator.

Exclusion from Bronchoscopy for 14 Days

The presence of any of the following characteristics that differentiate VSA from temporary exclusion will exclude for 14 days a subject from participating as a bronchoscopy volunteer:

Events occurring within 6 months of bronchoscopy

- Intubation for asthma within the past 6 months
- More than 12 exacerbations within the past 6 months

Events occurring within 6 weeks of bronchoscopy

- Hospitalization for asthma within the past 6 weeks

Events occurring within 2 weeks of bronchoscopy

- Increased oral corticosteroid use in the past 14 days, recognized as a dose which is both numerically at least twice that of baseline, and which is at least 20 mg/day greater than the baseline dose

Events occurring within 48 hours of bronchoscopy

- Pulse oximetry demonstrating oxygen saturation $< 90\%$ on room air
- Use of more than 16 puffs of a short acting β -agonist per day in the past 48 hours
- Significant increase in asthma symptoms in the past 48 hours, recognized as an increased use of short acting β -agonists of more than 8 puffs/day (more than 8 puffs/day over baseline)
- $FEV_1 < 40\%$ predicted after administration of 2.5 mg albuterol via nebulizer; n.b. the minimal operative FEV_1 may be higher than this absolute cutoff. See Table 9.3 for phase-in criteria.
- $FEV_1 < 35\%$ predicted before the administration of bronchodilator; n.b. the minimal operative FEV_1 may be higher than this absolute cutoff. See Table 9.3 for phase-in criteria.

Exclusion from Bronchoscopy for an Indefinite Period

The presence of clinically important comorbidities—these include uncontrolled diabetes, uncontrolled coronary artery disease, acute or chronic renal failure, and uncontrolled hypertension—that would increase the risk of significant adverse events during bronchoscopy represent exclusion criteria for bronchoscopy. If the comorbidity resolves, the subject's eligibility can be reevaluated. The clinical judgment of the investigator or bronchoscopist is required, and in those cases in which judgments must be made, bias towards subject safety is essential.

9.1.5 Medication for Bronchoscopy

As the details of medication are unlikely to affect shared samples, this aspect of the procedure is left to the discretion of the investigator and bronchoscopist.

Conscious sedation, delivered by IV medication, or light anxiolysis delivered by a route other than IV, may be employed at the discretion of the investigator and as approved by the IRB of the investigators. Clinical judgment is critically important for selecting and administering conscious sedation. Dose titration is the rule, rather than the exception, and fixed dosing regimens are neither commonly used clinically, nor biologically justifiable. For sites that use IV conscious sedation, all relevant local policies and the SARP procedures detailed in the *Manual of Procedures* (Section 9.2, p 118) will be observed.

For sites that use light parenteral sedation, we will offer this form of sedation to all subjects. If subjects refuse this sedation, we believe they may do so without compromise.

In subjects with VSA, IV access is recommended, whether or not IV conscious sedation is employed.

Table 9.4 lists commonly used medications and adult dose ranges.

Table 9.4: Medications for Bronchoscopy

Class	Drug	Dose Range
Anxiolytic	Midazolam (IM or IV)	0.5–10 mg
Bronchodilator	Albuterol (nebulized)	2.5–5 mg
Anticholinergic	Atropine (IM or IV)	0.4–0.6 mg
	Glycopyrrolate (IM or IV)	0.2–0.4 mg
Narcotic-Antitussive	Demerol (IM or IV)	50–100 mg
	Fentanyl (IM or IV)	25–250 μ g
	Codeine (IM or PO)	30–60 mg
	Alfentanyl (IM or IV)	250–500 μ g
	Morphine (IM or IV)	2–8 mg

9.1.6 Topical Anesthesia

As the details of topical anesthesia are unlikely to affect shared samples, this aspect of the procedure is left to the discretion of the investigator and bronchoscopist. The spirit of this guideline is to minimize the lidocaine dose delivered to the volunteer. For purposes of calculation, all lidocaine administered is to be included, whether delivery is via gargle, aerosol, spray, or instillation. For

subject safety, the

total lidocaine limit will be 600 mg.

This limit is based on a recent publication¹ that demonstrates the safety of this dosing regimen and acceptable serum lidocaine levels. If this limit is exceeded, a serum lidocaine level should be obtained and the subject observed. The amount of lidocaine used should be recorded in the procedure record sheet.

9.1.7 Procedural Monitoring

If no IV conscious sedation is employed, minimum monitoring includes O₂ saturation and heart rate.

If IV conscious sedation is employed, minimum monitoring includes O₂ saturation, heart rate, BP, and ECG. If conscious sedation is employed, all local policies relevant to conscious sedation should be observed.

Note: if *any sedation* is administered, follow post-bronchoscopy procedures for the subject's disease classification as described in this *Manual of Procedures*.

Personnel Recommendations

To ensure subject safety, and to facilitate appropriate processing of samples, the following minimum in suite personnel are recommended for all procedures:

- Bronchoscopist
- Bronchoscopy Assistant (Nurse, RT, or trained technician); this person should assist the bronchoscopist in monitoring the subject for signs of physiologic distress
- Sample handler
- In subjects with VSA, an additional trained individual is recommended; the sole task of this person is to monitor vital signs, oximetry, and other physiologic and clinical signs to ensure subject safety.

Procedural Documentation

In all cases, documentation of details of the procedure is required. Use of a site-specific standard form for all procedures is strongly encouraged, in order to capture all relevant clinical issues; the details of the form will be institution specific. An appropriate form is available from the DCC website. The following information should be captured:

¹Langmack EL, et al. *Chest* 2000; 117: 1055–60.

Prior to Bronchoscopy

Subject status: HC, MMA, SA, VSA, COPD
 Mental status
 Pulmonary examination
 Vital signs
 Baseline pulse oximetry
 Investigator review of recent H&P and *SARP Prebronch Checklist*

Note: For subjects with VSA, or for subjects for whom the bronchoscopist or investigator determines an *a priori* need for overnight hospitalization and monitoring, *documentation of this decision before the procedure* is essential to avoid the requirement to report such hospitalization as a serious Adverse event.

Procedural Details

Bronchoscopist and assistants
 Premedications: dose and route
 Topical anesthesia: type, dose
 Route (oral or nasal)
 Appearance of vocal cords
 Sites of procedures (BAL, brushings, biopsies)
 BAL: aliquot size (standard at 50ml), number (standard 2), volume return
 Bronchial brushings: location
 Biopsies: number and location

Procedural Monitoring

O₂ saturation and heart rate
 Add BP and ECG if conscious sedation is used

Postprocedure

Document acceptable O₂ saturation on room air
 Document FEV₁ within 15% of prebronchoscopy, prealbuterol value
 Document 24/7-valid contact info provided to volunteer
 Document determination of need for extended 12+ hour monitoring or hospitalization
 (see Sections 9.1.13 and 9.1.14)

9.1.8 Approach

The selection of transoral or transnasal approach will be left to the discretion and judgment of the bronchoscopist, based on individual subject characteristics and anatomy, choice of bronchoscope, and other local considerations. The approach route must be documented in the procedure record.

9.1.9 Bronchoalveolar Lavage: Performance

Bronchoalveolar lavage will often be the first procedure performed (of BAL, brushings, and biopsies) because the latter two generate trauma which will contaminate BAL fluids, even if the BAL is performed in a segment distinct

from the brushings or biopsies. However, the needs and preferences of the individual investigators should be honored. If biopsies are performed prior to BAL, care must be taken to clear the working channel of the bronchoscope of contaminating blood and other debris.

Shareable samples of BAL should be obtained prior to bronchial brushings or bronchial biopsy, or taken from a different segment, and preferably a different lobe, in order to avoid contamination of the sample with blood.

In order to ensure maximal volume return, fluid to be used for BAL will be warmed (37°C). Instillation of fluid will occur using hand pressure on a syringe, and the fluid will be recovered into the same syringe using hand suction to minimize mucosal trauma and contamination of BAL fluid with serum proteins.

BAL will employ 50 ml aliquots. The standard technique will be instillation and recovery of one aliquot, followed by instillation and recovery of the second aliquot. If the recovered volume is < 15 ml from the first 100 ml of injectate, then the BAL will be stopped. The return from these 2 syringes will be pooled, and the supernatant recovered for analysis. Investigators who choose to use higher volume BAL are free to do so with additional 50 ml aliquots. However, the combined return from the first two, as noted above, will be considered the standard *shareable samples* BAL material.

Standard technique will be to use two 50-ml aliquots, pooled and frozen; additional aliquots may be obtained from the same segment at the discretion of the investigator, based on the needs of the study. Further, additional segments may be used, again at the discretion of the bronchoscopist.

9.1.10 Bronchoalveolar Lavage: Processing

The return from the first 2 syringes will be pooled. No straining of fluid through gauze or wire mesh should be performed, in order to minimize loss of cells. Fluid is centrifuged to recover cell pellet. The excess of the supernatant beyond the needs of the investigator is aliquoted in as many as ten 1-ml samples (*shareable samples*). An additional 1 ml aliquot may be prepared for the Cleveland site. Another additional 1 ml aliquot, mixed with an equal volume of ice cold methanol, may be prepared for the Boston site.

The cell pellet is resuspended, cell counts are performed, and 12 cytocentrifuge slides are prepared. Two are stained with Diff-Quick or other histological stain and are interpreted for cellular differential. From this information, total and differential cell counts are computed. Of the other 10 slides, 5 are fixed in acetone, and 5 are fixed in 0.5% formalin; these latter 10 slides represent *shareable samples*.

9.1.11 Bronchial Brushings

In most circumstances, BAL procedures should be completed prior to brushings, in order not to contaminate the BAL with red blood cells or other brush-related traumatic artifacts.

Locale of brushing is at the discretion of bronchoscopist, but typically is performed in a lower lobe segment, with 10 fore-and-aft strokes performed to dislodge epithelial cells. Cells may be dislodged by agitation in sterile media, and recovered by centrifugation, or by preparing a direct smear onto a sterile slide.

Epithelial cells in excess of those required for the project of the investigator may be used to prepare *shareable samples*. To do so, prepare up to 4 cytocentrifuge slides with 50,000 to 75,000 cells per 0.5 ml, or 200,000 to 300,000 cells total). Fix 2 in methanol. Fix 2 in 0.5% paraformaldehyde. An additional slide may be prepared by smearing the brush across a glass slide, and fixing with 0.5% paraformaldehyde (Cleveland site).

9.1.12 Bronchial Biopsy

Bronchial biopsy is usually performed after BAL; however, the specific order or procedures may vary site-to-site depending on the specific needs of the project at the site. Locale for biopsy is at the discretion of the bronchoscopist. Endobronchial biopsies should be performed under direct vision, rather than blindly. The DSMB recommends that the location from which biopsies are taken be recorded in the procedure record. Transbronchial lung biopsy is a single-institution technique, and will not be addressed herein.

Forceps should be sharp; disposable units are preferable. Alligator forceps are preferred to cup forceps due to less crush artifact, and larger sample size. Any biopsies in excess of those required by the investigator may be prepared as *shareable samples*. These will be lightly fixed in acetone, and embedded in GMA; an additional sample may be formalin fixed and embedded in paraffin, per protocols to be posted on the SARP web site at later date. Shareable sample biopsies will be retained en bloc, and should not be pre-cut into sections.

It is recommended, if sufficient biopsy material exists, that sections be prepared at 2 μm thickness, 4 μm apart, and stained using monoclonal antibodies to recognize CD4, EG2, CD68, tryptase and neutrophil elastase positive cells (T-cells, activated eosinophils, macrophages, mast cells, and neutrophils). This information is useful to characterize the biopsy.

9.1.13 Postprocedure Follow-up and Monitoring

One hour minimum recovery time is recommended; two hours minimum recovery time is suggested if conscious sedation is used. Subjects with VSA will be hospitalized overnight, by protocol; thus, hospitalization in this group *does not* constitute a Serious Adverse Event. This requirement will be reconsidered after 6 months, in conjunction with the DSMB.

For subjects with severe or very severe asthma, albuterol 2.5 mg by nebulizer should be administered as soon as practical following the procedure. In subjects with very severe asthma, this dose is mandatory. In subjects with severe asthma, this dose may be omitted if all of the following are satisfied: the subject is symptom-free, not wheezing, and if tachycardia of more than 30 bpm above baseline heart rate is present. For other subjects, the administration of inhaled β -agonist following the procedure will be guided by clinical need, and the presence and degree of airflow limitation.

Assessment for the presence of hospitalization indicators (Section 9.1.14) should be made. If any are present, the subject should be hospitalized overnight. If the decision to hospitalize was not made prior to the procedure, the development of hospitalization indicators, and subsequent hospitalization, *does* constitute a serious adverse event.

Postbronchoscopy spirometry should be measured; for subjects other than VSA, the subject may be discharged following the minimum recovery time if FEV₁ reaches $\geq 85\%$ of that observed in the prealbuterol spirometry obtained prior to bronchoscopy (*Spirometry 2*).

Despite appropriate selection, preparation, procedural technique, postbronchoscopy monitoring, and physiologic assessment prior to discharge, it is possible that subjects occasionally will require urgent care following discharge from the procedure unit. Infrastructure should be in place to recognize the need for, and to facilitate, such care should the need arise.

Contact numbers must be provided to the subject. A follow-up call will be made to each subject with severe asthma or very severe asthma daily for three days. Other participants will receive one phone call the day after the procedure. In the unlikely event that postbronchoscopy concerns or issues have not resolved at the end of the scheduled contacts, ongoing contact and clinical care should be provided until the matter is appropriately resolved.

Adverse events should be documented. Serious unexpected adverse events, such as unexpected hospitalization or prolongation thereof, a life-threatening event, death, must be reported to the DCC and DSMB within 24 hours of the

investigator becoming aware of the event.

9.1.14 Hospitalization Indicators

Overnight hospitalization is mandatory for all subjects with VSA.

For any subjects who exhibit any of the following characteristics during or after bronchoscopy, overnight hospitalization should be provided:

- Significant cough persisting beyond 2 hours after completion of procedure
- Failure of PFTs after bronchodilator administration to return to within 15% of prebronchodilation FEV₁ at end of monitoring time
- Persistent hypoxia < 90% at end of monitoring time
- Persistent tachycardia > 130 bpm at end of monitoring time
- Unexpected altered mental status during or after procedure
- Significant hemoptysis > 50 ml
- Requirement for bronchodilator every 2 hours on more than 3 occasions
- In subjects with severe asthma, the unexpected absence of a companion or caretaker at home

Treatment should be directed towards resolving underlying airway obstruction and other pathophysiology, and relieving symptoms, based on the best clinical judgment of the physicians involved.

Follow-up telephone contact should be made for all subjects 24 hours after the procedure is completed. For subjects with SA and VSA, daily telephone contact for 3 days should be made. If issues have not resolved in either group at the time of the last scheduled contact, additional contact and necessary medical care should be arranged.

9.1.15 Maintenance and Equipment Matters

Consideration should be given to performing surveillance cultures of nominally sterile bronchoscopes on a periodic basis (3–6 month intervals) to ensure the adequacy of decontamination and sterilization procedures, consistent with local infection control policies. All relevant manufacturer recommendations about cleaning, maintenance, leak testing, and other issues should be followed.

9.2 Safety Algorithm

9.2.1 Part 1: Physiology

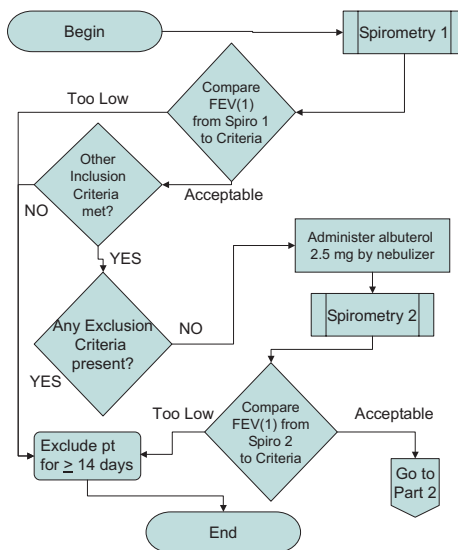


Figure 9.2: Bronchoscopy Safety Algorithm: Physiology. See Sections 9.1.3 and 9.1.4 for inclusion and exclusion criteria. See Table 9.3 for FEV₁ criteria.

9.2.2 Part 2: SA/VSA Determination

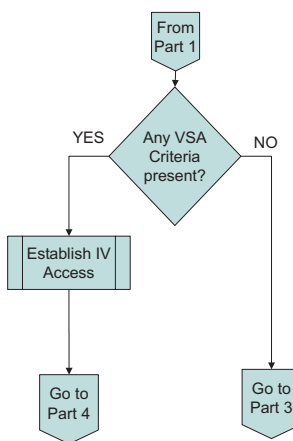


Figure 9.3: Bronchoscopy Safety Algorithm: SA/VSA Determination. See Section 9.1.3 for VSA criteria.

9.2.3 Part 3: IV Access in SA

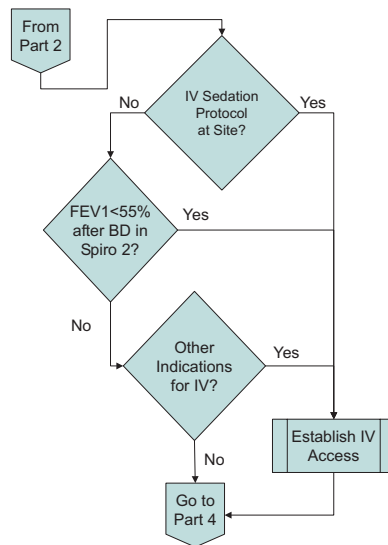


Figure 9.4: Bronchoscopy Safety Algorithm: IV Access in SA

9.2.4 Part 4: Procedure and Monitoring

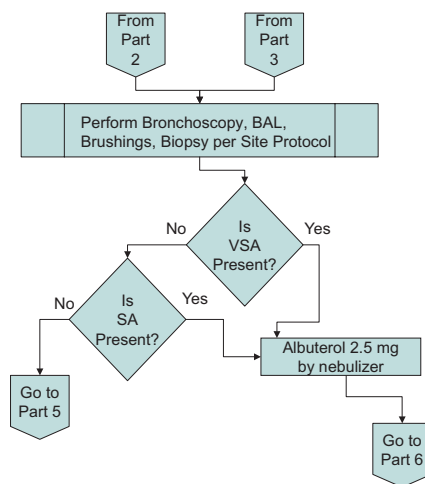


Figure 9.5: Bronchoscopy Safety Algorithm: Procedure and Monitoring

9.2.5 Part 5: Standard Care and Follow-up

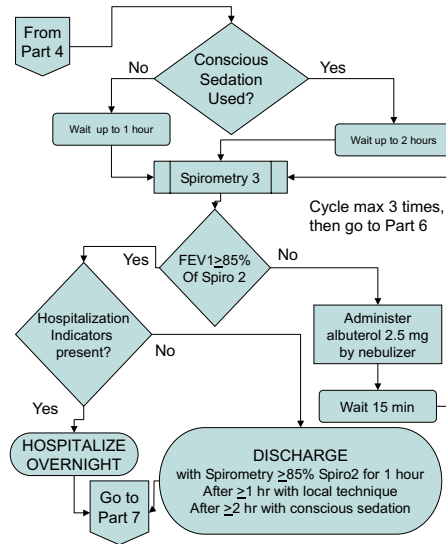


Figure 9.6: Bronchoscopy Safety Algorithm: Standard Care and Follow-up

9.2.6 Part 6: Higher Risk Care and Follow-up

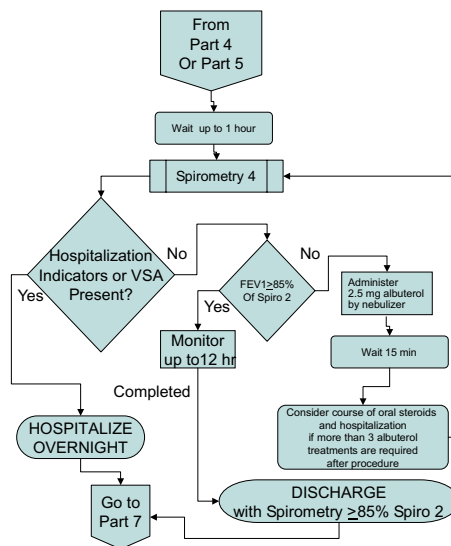


Figure 9.7: Bronchoscopy Safety Algorithm: Higher Risk Care and Follow-up

9.2.7 Part 7: Postbronchoscopy Follow-up

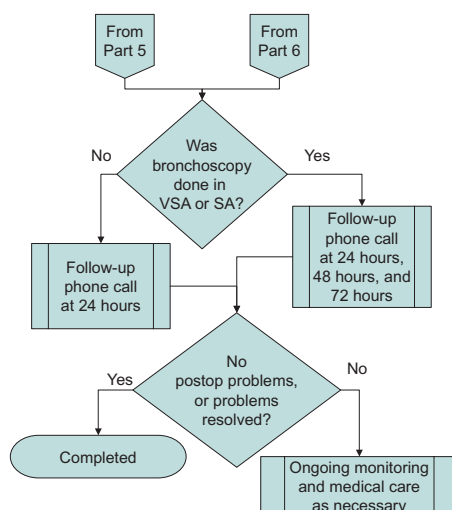


Figure 9.8: Bronchoscopy Safety Algorithm: Postbronchoscopy Follow-up

9.3 Pediatric Standards: 6–11 Years of Age

Children 6–11 years of age will not undergo bronchoscopy for research purposes. This section describes only the conditions under which samples obtained during a pediatric bronchoscopy performed exclusively for clinical purposes may be used and shared for research.

9.3.1 General Considerations

Children 6–11 years of age with severe asthma may require bronchoscopy for indications such as suspicion of foreign body, suspicion of infection, immotile cilia syndrome, congenital lesions of the airway, chronic aspiration, or persistent atelectasis. The indications for, timing of, anesthesia for, monitoring of, and recovery after these bronchoscopies are clinical decisions. General anesthesia or conscious sedation will be given to children 6–11 years of age; the physician who does the clinical bronchoscopy will determine the mode of anesthesia. Table 9.5 (p 127) lists common medications and dose ranges for these pediatric subjects. The guidelines for anesthesia and monitoring will be at least as stringent (generally substantially more stringent) than those for adults. Appropriate sites for doing bronchoscopy in pediatric subjects with severe asthma will be restricted to those with sufficient monitoring and staff suitable for the routine care of a child with a life-threatening respiratory illness.

9.3.2 Bronchoscopy Samples

Children aged 6–11 years will not have endobronchial biopsies for research purposes. The legal guardian(s) of 6–11-year-old children who undergo endobronchial biopsy for standard clinical indications and who meet SARP criteria will be asked to provide informed consent in order to share tissue with SARP investigators as follows:

- Standard clinical indications for endobronchial biopsy in children include diagnosis of immotile cilia syndrome, endobronchial tuberculosis, and histopathology of unknown endobronchial lesions.
- At least 6 tissue fragments will be submitted to the clinical pathology laboratory for fixation and analysis. Any tissue that remains after standard histopathological evaluation can be shared with SARP investigators.
- Specific contraindications to endobronchial biopsy are suspected vascular tumors of the airway (carcinoid), platelet count less than $50,000 \text{ mm}^3$, and a known coagulation disorder.

In this way, tissue samples will be taken only when indicated for clinical diagnostic purposes.

9.3.3 Informed Consent

Two consents will be obtained. One will be the standard institution clinical procedure consent form. Under no circumstances will this consent form be obtained or signed by an investigator involved in the SARP. A separate consent, approved by the Institutional Review Board (IRB), will be obtained for using extra clinical specimens for research purposes. This consent will be obtained by a SARP-associated investigator. It will contain at least the following information:

- The procedure is not being performed for research purposes.
- The purpose of this study is to define what kind of chemical imbalances in the airway lead to severe asthma. The child is being included because he or she has asthma.
- Extra samples are not being obtained for research purposes.
- Standard procedures for lavage and, if indicated, biopsy will be used (if there is any extra fluid or tissue after adequate samples have been sent for clinical analysis, the parent or guardian consents for these to be used for research purposes).
- These samples may be shared with other centers in the SARP.

- The parent or guardian is free to choose not to participate in the study. Choosing not to participate will in no way alter the child's care.
- Because no additional procedures are being done for research purposes, participation does not add risk to the procedure.
- Information about participation in the study will be placed in the child's medical record. Officials of the Food and Drug Administration, local IRB, or NIH may have access to these records. Information may also be published, but the child will not be able to be identified in the publication.
- There is no specific benefit to the child's participation. The benefit to society is that childhood asthma may be better understood.
- There is no financial compensation for participation.

9.3.4 Unique Procedural Issues in Pediatrics

It will be preferred that standard bronchoalveolar lavage technique for asthma will be used. The bronchoalveolar lavage fluid should be warmed to 37°C. For children at least 12 years old, two 50-ml aliquots, pooled, will be ideal. For children less than 12, the aliquot volume will ideally be 1 ml/kg. The clinical bronchoscopist will determine how he or she wants the specimens used. Then, if there is any remaining specimen, the SARP investigator will be called and will have the option of triaging the sample to be processed as outlined in the adult protocol above, with the caveat that there will be much less sample and experiments of local relevance may take precedence.

9.4 Pediatric Standards: 12–17 Years of Age

9.4.1 Purpose

It is the primary goal of this document to provide collective experience and advice of the participating centers, in order to maximize the safety of pediatric subjects aged 12–17 years that participate as volunteers in the Severe Asthma Research Program. An important secondary goal is to facilitate the acquisition of airway samples (BAL fluid, BAL cells, bronchial brushings, and bronchial biopsies) that can be shared with other SARP investigators. This document is separate from the Standards proposed for adults and children 6–11 years of age.

Bronchoscopy in 12–17-year-old children will be performed for research purposes only or when clinically indicated and permission is obtained for additional research samples. It is our opinion that research studies in this age group are

needed to further our understanding of severe asthma. Conclusions which are simply extrapolated from adults, may be misleading. Therefore, in this group of 12–17-year-old children, the benefits of research bronchoscopy outweigh the potential risks.

9.4.2 General Considerations

Subjects must meet all inclusion criteria (Section 9.4.3) and not meet any exclusion criteria (Section 9.4.4).

Considerations for all subjects

- Ability to cooperate with procedure
- Ability to give consent (parents of pediatric subjects) and assent (pediatrics)
- Clotting studies, CBC, and platelet counts may be done as a bronchoscopy screen at the discretion of investigators, but are not required.
- Coexisting lung disease

Considerations for asthmatic subjects

- Clinical stability, with no evidence of viral infection or exacerbation, consistent with the specific inclusion and exclusion criteria outlined below. A subject judged to be clinically unstable by the investigator or bronchoscopist should generally be excluded from bronchoscopy until acceptable clinical stability, as defined in the inclusion (Section 9.4.3) and exclusion (Sections 9.4.4 and 9.4.5) criteria, is achieved.
- Consideration should be given to overnight monitoring and observation in subjects with a history of frequent exacerbations (5 exacerbations in the previous 180 days)
- For all pediatric participants with severe asthma, a competent companion or caretaker should be available at home for at least 24 hours after the procedure. Identification of such a person should precede initiation of sedation and bronchoscopy.

Considerations about consent and assent

- In order to assure that participants and their parents have ample opportunity to review study related materials before the initial study visit, once a participant is scheduled for an initial visit, a packet of materials will be mailed to the participant's home. This packet will include the informed

consent document, the assent document, and other study-related information. The child and parent will have at least 48 hours to review this material in order to help them generate further questions they may have regarding study participation. They will be provided with a telephone number to call to ask any questions they have regarding the study and the consent and assent forms. In addition, a study investigator will call the family 24 hours before the visit to review the consent and assent forms and encourage any questions. The investigator will again be present to review the consent and assent forms at the time of the first visit and address any further questions or concerns.

- In addition to reviewing these documents, the investigator and study coordinator will reinforce that participation in the study is entirely voluntary. Participants may choose not to enroll, or they may withdraw at any time. Refusal to enroll or withdrawal will not affect the care they receive regarding their child's asthma.
- The investigator will discuss the risks and benefits with the child and will obtain written assent when required to do so by the local IRB.

9.4.3 Specific Inclusion Criteria

Subjects must meet each of the following criteria in order to qualify for the bronchoscopic study:

- PFT: Prebronchodilator FEV_1 in *Spirometry 1*, obtained before bronchodilator administration, must always be $\geq 45\%$ of predicted.
- PFT: Postbronchodilator FEV_1 in *Spirometry 2* obtained after administration of 2.5 mg albuterol by nebulizer must always be $\geq 55\%$ of predicted.
- Age: 12–17 years
- Gender: no selection criteria
- Minority status: no selection criteria
- No hospitalization for asthma in the previous 6 months and no intubation for asthma in the previous 12 months
- Subject must be judged otherwise to be clinically appropriate for bronchoscopy by the bronchoscopist. No specific PFT or other criteria, other than above, are used to document subject's clinical stability. Safety of the subject is the overriding concern in making this determination. Details of the clinical course must be detailed in the record.

9.4.4 General Exclusion Criteria

- Inability to provide informed consent (adult) or assent (pediatrics)
- Inability or unwillingness to complete scheduled SARP procedures
- Lack of reliable communications channel (hard-wire phone, cell phone, email for follow-up contacts after bronchoscopy)

9.4.5 Specific Exclusion Criteria

Subjects with very severe asthma, as defined in the *Adult Bronchoscopy Standards* (Section 9.1), and subjects with a current asthma exacerbation are specifically excluded from pediatric bronchoscopy. Those experiencing an asthma exacerbation may be reevaluated in 14 days. The following exclusion criterion should exclude a subject from enrollment:

- More than 6 exacerbations in the previous 6 months
- Hospitalization for asthma in the previous 6 months
- Intubation for asthma in the previous 12 months
- Pulse oximetry on room air showing oxygen saturation of $< 90\%$
- Use of more than 8 puffs of a short-acting β -agonist per day
- In the presence of a regular long-acting β -agonist, the use of a short-acting β -agonist in excess of 4 puffs per day
- Regular corticosteroid dose of ≥ 20 mg/day
- Significant increase in asthma symptoms in the previous 48 hours, recognized as an increased use of a short acting β -agonist of more than 8 puffs/day over baseline
- A changed dose of oral corticosteroid (up or down) in the previous 14 days
- Current asthma exacerbation or other clinical instability in the judgment of the investigator or bronchoscopist
- If necessary, D_{LCO} can be performed at the discretion of the investigator to clarify the diagnosis of very severe asthma. In this setting, a D_{LCO} less than 70% predicted will be exclusionary. However, determination of D_{LCO} is not mandatory.
- The presence of clinically important comorbidities—these include uncontrolled diabetes, uncontrolled heart disease, acute or chronic renal failure, and uncontrolled hypertension—that increase the risk of significant adverse

events during bronchoscopy. The clinical judgment of the investigator or bronchoscopist is required, and in those cases in which judgments must be made, bias toward subject safety is essential.

9.4.6 Medication for Bronchoscopy

As the details of premedication are unlikely to affect shared samples, this aspect of the procedure is left to the discretion of the investigator and the bronchoscopist, as approved by the IRB of the investigator. Conscious sedation, delivered by IV or by mouth in a manner consistent with local guidelines on conscious sedation, will be given to all pediatric subjects 12–17 years of age.

Clinical judgment is critically important to select and administer conscious sedation. Dose titration is the rule rather than the exception, and fixed dosing regimens are neither commonly used clinically, nor biologically justifiable.

Table 9.5 lists common medications and dose ranges for pediatric subjects 6–17 years of age.

Table 9.5: Common Medications and Pediatric Dose Ranges

Class	Drug	Dose Range
Anxiolytic	Midazolam	0.025–0.050 mg/kg*
Anticholinergic	Atropine	0.01–0.02 mg/kg
	Glycopyrrolate	8 μ g/kg
β -adrenergic	Albuterol	1–5 mg
Narcotic-Antitussive	Demerol	1.0–2.2 mg/kg
	Fentanyl	1–2 μ g/kg/dose†
	Codeine	10–20 mg
	Morphine	0.1–0.2 mg/kg

* Carefully titrate dose; the usual maximum dose is 10 mg, but as much as 0.4 mg/kg may be required.

† May repeat at 30-min intervals up to 4 μ g/kg

9.4.7 Topical Anesthesia

As the details of topical anesthesia are unlikely to affect shared samples, this aspect of the procedure is left to the discretion of the investigator and the bronchoscopist. The spirit of this guideline is to minimize the lidocaine dose delivered to the volunteer. For purposes of calculation, all lidocaine administered is to be included, whether delivery is via gargle, aerosol, spray, or instillation. For

subject safety, the following guidelines on lidocaine dose are suggested:

Lidocaine will be administered at a target dose range of 5–7 mg/kg over a 30-minute period. In unusual circumstances, however, a dose of up to 8–9 mg/kg may be required.

The amount of lidocaine used should be recorded in the procedure record sheet.

9.4.8 Procedural Monitoring

Because IV conscious sedation is employed, minimum monitoring includes

O₂ saturation, heart rate, BP, and ECG .

In addition, all local policies concerning conscious sedation should be observed.

All participants will receive supplemental oxygen (e.g., ≥ 2 liters/min) during the procedure. Persistent hypoxia of less than 92% oxygen saturation at end of monitoring will result in hospitalization; see Section 9.4.17 for all indicators of hospitalization.

9.4.9 Personnel Recommendations

To ensure subject safety and to facilitate appropriate processing of samples, the following minimum in suite personnel are recommended for all procedures:

- Bronchoscopist with pediatric experience
- Bronchoscopy assistant (a nurse, RT, or trained technician); this person will assist the bronchoscopist in monitoring the subject for signs of physiologic distress
- A second bronchoscopy assistant: an additional clinically trained individual in the bronchoscopy suite is recommended; this person's sole responsibility is to monitor vital signs, oximetry, and other physiological and clinical signs to ensure subject safety.
- Sample handler

9.4.10 Procedural Documentation

In all cases, documentation of details of procedure is required. Use of a site-specific standard form for all procedures is strongly encouraged in order to capture all relevant clinical issues; the details of the form will be institution-specific. An appropriate form is available from the DCC website. The following information should be captured:

Prior to Bronchoscopy

Mental status
 Pulmonary examination
 Vital signs
 Baseline pulse oximetry
 Investigator review of recent H&P and *SARP Prebronch Checklist*
 Document 24/7-valid contact information provided to volunteer
 Document that an adult caregiver will be available after the procedure and discharge

Note: For subjects for whom the bronchoscopist or the investigator determines an *a priori* need for overnight hospitalization and monitoring, *documentation of this decision before the procedure* is essential to avoid the requirement to report such hospitalization as a serious adverse event.

Procedural Details

Bronchoscopist and assistants
 Premedications: dose and route
 Topical anesthesia: type, dose
 Route (oral or nasal)
 Appearance of vocal cords
 Sites of procedures (BAL, brushings, biopsies)
 BAL: aliquot size, number of aliquots, total volume
 Bronchial brushings: location
 Biopsies: number and location

Procedural Monitoring

O₂ saturation, heart rate, BP, and ECG

Postprocedure

Document acceptable O₂ saturation on room air
 Document FEV₁ within 15% of prebronchoscopy, prealbuterol value
 Document 24/7-valid contact info provided to volunteer
 Document determination of need for extended 12+ hour monitoring or hospitalization
 (see Sections 9.4.16 and 9.4.17)

9.4.11 Approach

The selection of transoral or transnasal approach will be left to the discretion and judgment of the bronchoscopist, based on individual subject characteristics, anatomy, choice of bronchoscope, and other local considerations. The approach route must be documented in the procedure record.

9.4.12 Bronchoalveolar Lavage: Performance

Bronchoalveolar lavage (BAL) will often be the first procedure performed (of BAL, brushings, and biopsies) because the latter two generate trauma which

will contaminate BAL fluids, even if the BAL is performed in a segment distinct from the brushings or biopsies. However, the needs and preferences of the individual investigators should be honored. If biopsies are performed before BAL, care must be taken to clear the working channel of the bronchoscope of contaminating blood and other debris.

Shareable samples of BAL should be obtained before bronchial brushings or bronchial biopsy—or taken from a different segment, and preferably a different lobe—in order to avoid contamination of the sample with blood.

In order to ensure maximal volume return, fluid to be used for BAL will be warmed to 37°C. Instillation of fluid will occur using hand pressure on a syringe, and the fluid will be recovered into the same syringe using hand suction to minimize mucosal trauma and contamination of BAL fluid with serum proteins.

BAL will employ 1 ml of saline per kg in weight for each aliquot, repeated up to 4 times (maximum 4 cc/kg). The standard technique will be instillation and recovery of 1 aliquot, followed by instillation and recovery of each of the remaining aliquots. If the recovered volume is < 15 ml from the first 100 ml of injectate, then the BAL will be stopped. The return from these syringes will be pooled, and the supernatant removed and frozen. The return from the first 2 aliquots will be considered the standard *shareable sample* BAL material.

9.4.13 Bronchoalveolar Lavage: Processing

The return from the first 2 syringes will be pooled. No straining of fluid through gauze or wire mesh should be performed, in order to minimize loss of cells. Fluid is centrifuged to recover cell pellet. Excess supernatant is aliquoted to ten 1-ml samples (*shareable samples*). An additional 1-ml aliquot can be prepared with an antioxidant cocktail for the Cleveland site. An additional 1-ml aliquot mixed with an equal volume of ice cold methanol can be prepared for the Boston site.

The cell pellet is resuspended, cell counts are performed, and 12 cytocentrifuge slides are prepared. Two are stained with Diff-Quick or other histological stain and are interpreted for cellular differential. From this information, total and differential cell counts are computed. Of the other 10 slides, 5 are fixed in acetone, and 5 are fixed in 0.5% formalin; these latter 10 slides represent *shareable samples*.

9.4.14 Bronchial Brushings

In most circumstances, all required BAL procedures should be completed before brushings in order not to contaminate the BAL with red blood cells or other

brush-related traumatic artifacts.

Locale of brushing is at the discretion of the bronchoscopist, but typically it is done in a lower lobe segment, with 10 fore-and-aft strokes to dislodge epithelial cells. Cells can be dislodged by agitation in sterile media and recovered by centrifugation or by preparing a direct smear onto a sterile slide.

Epithelial cells in excess of those required for the project of the investigator may be used to prepare *shareable samples*. To do so, prepare 4 cytocentrifuge slides with 50,000 to 75,000 cells per 0.5 ml, or 200,000 to 300,000 cells total). Fix 2 in methanol. Fix 2 in 0.5% paraformaldehyde. An additional slide may be prepared by smearing the brush across a glass slide, and fixing with 0.5% paraformaldehyde (Cleveland site).

9.4.15 Bronchial Biopsy

Bronchial biopsy is performed after BAL. Specific locale is at the discretion of the bronchoscopist. Endobronchial biopsies should be performed under direct vision rather than blindly. The location from which biopsies are taken should be recorded in the procedure record. Transbronchial lung biopsy is a single-institution technique and will not be addressed herein.

Forceps should be sharp; disposable units are preferable. Alligator forceps are preferred to cup forceps due to less crush artifact and larger sample size.

Any biopsies in excess of those required by the investigator may be prepared as *shareable samples*. These will be lightly fixed in acetone and embedded in GMA; an additional sample may be formalin-fixed and embedded in paraffin according to protocols that will be posted on the SARP website at a later date. Shareable-sample biopsies will be retained en bloc, and should not be precut into sections.

It is recommended, if sufficient biopsy material exists, that sections be prepared at 2 μm thickness, 4 μm apart, and stained using monoclonal antibodies to recognize CD4, EG2, CD68, tryptase, and neutrophil elastase positive cells (T-cells, activated eosinophils, macrophages, mast cells, and neutrophils). This information is useful to characterize the biopsy.

9.4.16 Postprocedure Follow-up and Monitoring

Two-hour minimum recovery time is recommended after conscious sedation. For those subjects with a history of exacerbation within 30 days, monitoring up to 12 hours by trained personnel—under the supervision of, with immediate access to—a physician is recommended.

The administration of inhaled β -agonist after the procedure will be guided by clinical need as well as the presence and degree of airflow limitation.

Assessment for the presence of hospitalization indicators (Section 9.4.17) should be made. If any indicators are present, the subject should be hospitalized overnight. If the decision to hospitalize was not made before the procedure, the development of hospitalization indicators and the subsequent hospitalization constitutes a serious adverse event.

Despite appropriate selection, preparation, procedural technique, postbronchoscopy monitoring, and physiological assessment before discharge, it is possible that subjects occasionally will require urgent care following discharge from the procedure unit. Infrastructure should be in place to recognize the need for, and to facilitate, such care should the need arise.

Postbronchoscopy spirometry must be measured: a subject may be discharged if FEV₁ reaches > 85% of that observed in the prealbuterol spirometry obtained before bronchoscopy (*Spirometry 2*).

In the unlikely event that postbronchoscopy concerns or issues have not resolved at the end of the scheduled contacts, on-going contact and clinical care should be provided until the matter is appropriately resolved.

Adverse events should be documented. Serious unexpected adverse events, such as unexpected hospitalization or prolongation thereof, a life-threatening event, or death must be reported to the DCC and to the DSMB within 24 hours of the investigator learning of the event.

Contact numbers must be provided to the subject. Follow-up telephone calls will be made to each participant once a day for 3 days after the procedure.

9.4.17 Hospitalization Indicators

Consideration for overnight hospitalization should be given for subjects who exhibit any of the following characteristics during or after bronchoscopy:

- Significant cough persisting beyond 2 hours after completion of procedure
- Failure of PFTs to return to within 15% of prebronchodilation FEV₁ at end of monitoring time
- Persistent hypoxia < 92% at end of monitoring time
- Persistent tachycardia > 130 bpm at end of monitoring time
- Unexpected altered mental status during or after procedure
- Significant hemoptysis > 25 ml

- Unexpected absence of a companion or caretaker at home

Treatment should be directed toward resolving underlying airway obstruction and other pathophysiology and relieving symptoms, based on the best clinical judgment of the physicians involved.

9.4.18 Maintenance and Equipment Matters

Consideration should be given to performing surveillance cultures of nominally sterile bronchoscopes on a periodic basis (3–6 month intervals) to ensure the adequacy of decontamination and sterilization procedures, consistent with local infection control policies.

All relevant manufacturer recommendations about cleaning, maintenance, leak testing, and other issues should be followed.

9.5 Stopping Rules

9.5.1 Purpose

This section codifies policies for imposing a temporary moratorium on the conduct of bronchoscopies or specific bronchoscopic procedures at one or more of the SARP sites. These policies are designed to maximize subject safety and to minimize the occurrence of adverse events and serious adverse events. A moratorium can be general (implemented for all bronchoscopies and related procedures) or limited (implemented for a specific procedure: e.g., bronchoalveolar lavage, bronchial biopsy, or transbronchial biopsy).

There are specific stopping rules for transbronchial biopsy, a single-center procedure; these stopping rules are detailed in Section 9.6.4 (p 140) and are hereby incorporated by reference.

9.5.2 Existing Information about Adverse Events

In general, the current literature fails to establish the expected incidence of adverse events related to bronchoscopy. In published reports, there is considerable heterogeneity in patient populations studied, invasive procedures employed, and the vigor and thoroughness with which investigators identified adverse events. At present, there is insufficient experience within the SARP to provide accurate estimates of the expected frequencies of AEs and SAEs.

The SARP will use an aggressive approach to recognize and identify adverse events. We will use a process-driven approach to analysis and response to ad-

verse events that may occur during the SARP. Below, we define the process by which the Steering Committee will evaluate and respond to AEs and SAEs, and we propose 3 types of moratoria, and we describe the process by which moratoria are implemented and lifted.

9.5.3 Review of All Adverse Events

Each principal investigator is scientifically and ethically responsible for monitoring the occurrence of adverse events and severe adverse events at their site or center. If significant concerns about AEs or SAEs arise at a particular site or center, a local moratorium should be considered. In addition, the SARP Steering Committee, during its routine monthly telephone or in-person meetings, will review summary statistics on the occurrence of AEs and SAEs. After review, summary statistics and supporting details will be forwarded to the DSMB, along with a recommendation for specific action, if any action is deemed necessary.

On the occurrence of any SAE, the center or site will notify the DCC within 2 working days. The DCC will arrange for an urgent phone conference of a quorum of the Steering Committee to be held within 2 working days for discussion of the SAE. The recommendation for action of the Steering Committee from this phone conference as well as the details of the SAE will be forwarded to the DSMB for its review.

In addition, the SARP Steering Committee and DSMB will conduct an ongoing review and analysis of AE and SAE reports submitted by each site or center, and they will consider collectively data from the entire SARP. If the Steering Committee and DSMB are concerned about the results of such an analysis, they can impose one of 2 moratoria:

1. *a site- or center-specific moratorium*, if the review suggests that the matter is limited to one or more specific sites or centers, or
2. *a program-wide moratorium*, if the review suggests that the matter could be reasonably expected to affect all sites and centers in the SARP.

9.5.4 Types of Moratoria

Investigator-Initiated: Site- or Center-Specific

If an investigator learns of a local matter that could compromise subject safety or could increase the risk of an AE or SAE, they should impose a local, site- or center-specific moratorium on bronchoscopic procedures. An example of this moratorium would be the recognition of improper cleaning procedures for the

bronchoscopes, faulty procedures that contribute to an AE or SAE; the moratorium would be lifted after appropriate changes had been implemented.

Although the issue that triggers an investigator-initiated moratorium may involve other sites or centers, the moratorium does not impact formally other sites or centers. Nevertheless, each principal investigator should ascertain whether the circumstances that led to the moratorium are relevant at their site.

Steering Committee or DSMB-Initiated: Site- or Center-Specific

If the ongoing safety review by the Steering Committee or DSMB reveals an matter of concern that is likely or clearly related to a single site or center, the Board can impose a site- or center-specific moratorium on all procedures related to bronchoscopy. An example of this moratorium would be an unacceptably high rate of significant bleeding after bronchial biopsy at a single site or center; the moratorium would be lifted after the reasons were identified and corrective action taken.

Steering Committee or DSMB-Initiated: Program-Wide

An important component of adverse event monitoring is the identification of AEs, SAEs, and other events that may happen rarely at an individual site but happen more frequently across all SARP sites. If the collective incidence concerns the Steering Committee or the DSMB, a program-wide moratorium could result. In addition, an adverse event of major consequence—serious injury or death—could result in a program-wide moratorium imposed by the Steering Committee or DSMB.

9.5.5 Guidelines for Imposing a Moratorium

Investigator-Initiated: Site- or Center-Specific

A principal investigator should consider imposing a site- or center-specific moratorium if the following occurs:

- The principal investigator learns of a situation at their site or center that could compromise subject safety or that could increase the risk of an AE or SAE.

Within 3 working days, the principal investigator will notify the DCC of the moratorium; the DCC will notify the Steering Committee. A committee composed of the Chair of the Steering Committee, a representative from the DCC, and a representative from the NIH will determine the level of urgency of

the matter, the breadth of applicability to SARP, and the appropriate action: a referral to the DSMB, an urgent conference call of the Steering Committee, or an agenda item for the next scheduled Steering Committee conference call.

Steering Committee or DSMB-Initiated: Site- or Center-Specific

The Steering Committee or DSMB should consider imposing a site- or center-specific moratorium if either of the following occur:

- An equipment-related concern arises. In this case, the moratorium would apply to each site at which the equipment of concern is used.
- An analysis by the Steering Committee or DSMB demonstrates that AEs or SAEs occur at a single site or center.

The DSMB will notify the DCC, the Steering Committee, and the relevant investigators of the moratorium.

Steering Committee or DSMB-Initiated: Program-Wide

The Steering Committee or DSMB will impose immediately a program-wide moratorium if either of the following occur:

- Any death is related to, or likely related to, a SARP bronchoscopy or related procedure, or
- Cardiopulmonary instability or unexpected endotracheal intubation is related to, or likely related to, a SARP bronchoscopy or related procedure.

In this situation, the center must notify the DCC within one working day; the DCC will immediately notify the DSMB and the entire SARP that a program-wide moratorium has been imposed.

9.5.6 Summary of Monitoring and Responses to Adverse Events

Adverse Events

Each month, the DCC will prepare a summary of adverse events; this summary will be a formal agenda item on each monthly Steering Committee conference call. The summary along with any related Steering Committee concerns and recommendations will be forwarded to the DSMB for review and action.

Serious Adverse Events

Serious adverse events are defined in the Federal Register. Serious adverse events expected to occur occasionally as a result of bronchoscopy are outlined in the

Manual of Procedures and consent form; unexpected serious adverse events may also occur. Each month, the DCC will prepare a summary of serious adverse events; this summary will be a formal agenda item on each monthly Steering Committee conference call. The summary along with any related Steering Committee concerns and recommendations will be forwarded to the DSMB for review and action.

A serious adverse event related temporally to bronchoscopy will be reported to the DCC within 2 working days. The Steering Committee will convene by telephone within 2 working days after the DCC broadcasts the bronchoscopy-related adverse event; the Steering Committee will review details of the serious adverse event, prepare a response and recommendation, and subsequently forward all relevant information to the DSMB. A quorum of the Steering Committee is defined as representation by the Principal Investigator or a Coinvestigator from at least 5 of the 8 centers.

Severe Adverse Events

Death or significant cardiopulmonary instability with or without the need for endotracheal intubation related to bronchoscopy or one of its associated procedures, will be reported within 1 working day to the DCC, which will forward the information immediately to the DSMB and notify the entire SARP. A 48-hr program-wide moratorium will begin when the investigators receive notification from the DCC.

9.5.7 Procedure for Lifting a Moratorium

A moratorium may be lifted only after DSMB review of the detailed descriptions of the adverse events or severe adverse events and descriptions of the changes proposed to minimize the likelihood of their recurrence. In most cases, a change in procedures or a change in subject-selection criteria will be appropriate; the scope of these changes could be site-specific or program-wide.

9.6 Transbronchial Biopsies

9.6.1 Background

Considerable data support the presence of inflammatory and remodeling processes of the distal lung in asthma, but specific pathologic studies are limited. There are 3 published transbronchial biopsy studies—one in nocturnal asthma

and 2 in severe asthma—that suggest there is increased and altered inflammation in the distal lung.²

In addition, there appears to be a different response to inhaled medications in severe asthmatic patients, a response that might result from limited ability of these drugs to reach the distal lung. Therefore, studies of the distal lung could have considerable impact on treatment options for patients with severe asthma. In SARP, we propose to evaluate parenchymal-airway attachments in asthmatic subjects to determine whether abnormalities in elastin or myofibroblasts exist in the distal lung. These changes might modify contractility and collapsibility of the airways and might explain the loss of elastic recoil, phenomena that have been observed in patients with severe asthma. In SARP II, only the University of Pittsburgh will perform transbronchial biopsies to evaluate parenchymal-airway attachments.

For more than 10 years, Dr. Wenzel, now at the University of Pittsburgh, has done transbronchial biopsies in subjects with severe asthma for research purposes: nearly 100 bronchoscopies, resulting in 200–400 transbronchial biopsies, have been performed. During all these biopsies, just one small pneumothorax—10% of lung volume—occurred; the pneumothorax resolved with supportive, noninvasive management. There have been no episodes of clinically significant bleeding. Usually, coughing from transbronchial biopsy is less than with lavage. When endobronchial biopsy, transbronchial biopsy, and bronchoalveolar lavage are all done, the total length of the procedure is less than 30 minutes. Therefore, we propose that the risk-benefit ratio is acceptable in asthmatic subjects.

9.6.2 Inclusion and Exclusion Criteria

General inclusion and exclusion criteria for endobronchial biopsies follow those outlined in the *Bronchoscopy Standards*, Sections 9.1.3 (p 106) and 9.1.4 (p 109), of the *Manual of Procedures*. For ethical reasons, transbronchial biopsies will not be done in healthy control subjects.

Inclusion Criteria for Subjects with Severe Asthma

- PFT: Prebronchodilator FEV₁ must be > 50% of predicted
- PFT: Postbronchodilator FEV₁ must be > 60% of predicted
- Age: 18–55 years
- Clinically stable according to endobronchial biopsy criteria

²Am J Respir Crit Care Med 1996; 154: 1505–1510; Am J Respir Crit Care Med 1997; 156: 737–743; Eur Respir J 2002; 20: 254–259.

- Able to withhold bronchodilator for 4 hours: because bronchodilator will not be withheld before the procedure, this criterion is for safety only
- Undergoing a clinically indicated bronchoscopy
- Normal INR and platelet count

Inclusion Criteria for Subjects with Mild-to-Moderate Asthma

- PFT: Prebronchodilator FEV₁ must be > 55% of predicted
- PFT: Postbronchodilator FEV₁ must be > 70% of predicted
- Age: 18–55 years
- Clinically stable
- Normal INR and platelet count

9.6.3 Procedure

The preparation for transbronchial biopsies will follow the general principles outlined for endobronchial biopsies. Additional precautions such as the use of fluoroscopy, time of the procedure, limits to the procedure, and the requirement that 2 physicians be present throughout the procedure will be taken to ensure subject safety.

To optimize lung function, all studies will be done after 10 AM. Biopsies will be done using fluoroscopic guidance. In general, biopsies will be taken roughly 3 cm from the fluoroscopically imaged chest wall to enhance the ability to obtain small airway tissue.

The first 10 subjects in each group (severe and mild-moderate) will undergo only 2 procedures: transbronchial biopsy with endobronchial biopsy in the subjects with severe asthma and transbronchial biopsy with either endobronchial biopsy or lavage in the mild-moderate subjects, depending on the specific nature of the scientific protocol.

If we can demonstrate that 2 procedures are safe, we hope to do all 3 procedures—endobronchial biopsy, lavage, and transbronchial biopsy—in both groups of subjects in the future.

Four transbronchial biopsies will be taken during each procedure for subsequent research analysis. This is 30–50% of the standard number taken in diagnostic and interstitial lung disease studies. The smaller number of biopsies will lessen the incidence of bleeding and pneumothorax; in published studies, the

rate of pneumothorax ranges from 1–5%. Epinephrine is mixed and available if excessive bleeding occurs.

Two experienced physicians, a registered nurse, respiratory therapist, and research technician will be present during each transbronchial procedure.

The time of radiation exposure will be recorded during all studies to estimate radiation dose during each procedure. Current Pittsburgh equipment is expected to expose a subject to 3–4 mSv of radiation; this amounts to 9–12 months of background radiation in Pittsburgh. This dose has been approved by the University of Pittsburgh Institutional Review Board.

9.6.4 Monitoring

Chest x-rays will be done immediately after the procedure and after any change in symptoms. Initially, all transbronchial biopsy subjects will be monitored overnight in the GCRC. Postbronchoscopy lung function will be monitored and treated using the same criteria as outlined in the *Bronchoscopy Standards*. In the absence of a severe adverse event, we will submit to the DSMB a detailed safety report within 7 days of biopsy for each of the first 3 subjects.

The DCC, NIH, and DSMB will be notified within 24 hours of any significant bleeding (>50 ml) or pneumothorax, including small ones that do not require drainage. We will file detailed reports on the first 7 subjects and propose—if these subjects experience no problems—that consideration be given to including subjects with lower lung function.

Unless there is a larger-than-expected dose in the first several subjects, the dose of radiation received by the subjects will be recorded and, after 7 subjects, this information will be submitted to the DCC, NIH, and DSMB.

Stopping Rules

- Any death from transbronchial biopsy
- More than one pneumothorax in the first 10 subjects
- More than one episode of significant bleeding in the first 10 subjects

9.6.5 Consent Language

Bronchoscopy with Transbronchial Biopsy

As part of the bronchoscopy described above, small pieces of tissue can also be removed from the parts of your lung beyond the visual limits of the bronchoscope. This procedure will enable small pieces of tissue to be gathered from

the smaller airway and the alveolar sacs (known as the distal lung). This part of your lungs (the smaller airways and the alveolar sacs) is different from the large airways where the biopsies were taken for the first part of the procedure. To obtain biopsy tissue from the distal lung, the study has to be done in the radiology (x-ray) department so that the instrument used to do the biopsies can be seen on the x-ray. When the bronchoscopist determines that the instrument is in the distal region of the lungs, a small piece of tissue is removed. Four biopsies will be done for research purposes. [*Note:* This section is for asthmatic subjects older than 18 years of age.]

Risks

The risks of transbronchial biopsy are similar to those outlined above (see endobronchial biopsy), but in addition, include the risk of a pneumothorax, or collapsed lung. This occurs when the biopsy is taken too close to the envelope that surrounds the lung (the pleura), such that it is punctured. This causes the air to escape from the lungs into that space around the lungs, ‘collapsing’ the lung to various degrees. This occurs approximately 1–2% of the time. Most of the time, the air leak is small and you will be treated with oxygen and observation only. However, it is also possible that the collapse of the lung will be severe enough that it will require immediate treatment to remove the escaped air. The collapsed lung would be treated by inserting a small tube (a chest tube) between your ribs, to remove the air. A local anesthetic will be given prior to the insertion of the chest tube. This tube would likely remain in place for about 24 hours, and you would be hospitalized overnight (sometimes longer) at University Hospital. Rarely, a surgical procedure is needed to sew up the hole.

Occasionally, 1–2% of the time, there can be significant bleeding (more than 3 tablespoons) from a transbronchial biopsy. However, blood tests will be done before the test to screen for any abnormal bleeding problems.

Radiation Exposure

You will be exposed to x-ray radiation during the bronchoscopy. A chest x-ray will be taken after the procedure to make sure you do not have a collapsed lung. The amount of radiation from a fluoroscopy (the x-ray machine) used during the bronchoscopy is about 3 mSv per bronchoscopy. This is the same as the amount of normal background radiation exposure a person receives in 1 year living at sea level or in 9 months living in Colorado. The more radiation you

receive over your lifetime, the greater the risk of having cancerous tumors or of causing changes in genes. Changes in genes might cause abnormalities or disease in your future offspring. The radiation in this study is not expected to greatly increase these risks, but the exact increase in such risks is not known. Women who are or could be pregnant should not participate in this study nor should they receive unnecessary radiation. If you suspect that you are or may be pregnant, please tell the study personnel immediately. A lead shield will be placed (waist to mid-thigh) over the reproductive organs to protect these organs from exposure.

9.7 Approval to Proceed with Bronchoscopy

In order to ensure prompt collection and submission of data to the Data Coordinating Center, each Center must contact the DCC before it bronchoscopes a given subject. When a Center provides the subject ID to the DCC, the DCC confirms that data from these forms are in the SARP database:

- Asthma Quality of Life Questionnaire
- Screening Questionnaire for Severe Asthma
- Atopic Diseases
- Demographic Information
- Environmental Factors
- Family History
- General Symptoms of Lung Disease
- Medical History
- Medication History
- Provoking Factors of Asthma and Lung Disease
- Smoking History
- Maximum Postbronchodilator Value of Lung Function

If all forms for the subject have been submitted to the DCC, the DCC relays approval to proceed with bronchoscopy to the Center. If one or more form is not in the database, the DCC identifies the forms(s) that must be submitted before the bronchoscopy can proceed.