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March 5, 1985

PIOPED PROTOCOL

PROSPECTIVE INVESTIGATION OF PULMONARY EMBOLISM DIAGNOSIS

NOTICE

The contents of this Protocol are confidential and are not to be discussed or quoted to persons other than those to whom this Protocol has been circulated.

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TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

EXHIBITS

CHAPTER 1

BACKGROUND AND STUDY RATIONALE

1.1 SCOPE

This study will address the problem of quantitatively evaluating non-invasive tests and clinical observations in the diagnosis of pulmonary embolism. Quantitative evaluation is essential to scientific progress in accurate diagnosis. The investigators propose to bring together techniques from internal medicine, nuclear medicine, angiography, biostatistics, and epidemiology to complete their quantitative evaluation. Chapter 1 presents a review of the literature on and problems in the quantitative evaluation of non-invasive tests and clinical observations in the diagnosis of pulmonary embolism. Chapter 2 states the objectives of this study and the design plans to meet these objectives by building on the experiences reported in Chapter 1 and solving the problems reviewed in Chapter 1. Chapters 3-14 describe how the study design will be satisfied by study procedures.

1.2 INTRODUCTION

Pulmonary embolism is a disease which has been recognized only in the last century and a half. In 1856 Virchow elucidated the pathophysiology of venous thrombosis and embolism (1). Before Virchow, medical teaching held that thrombosis induced phlebitis and that occlusions in pulmonary vessels originated from thrombi in situ. Early this century Osler focused on symptomatic hemorrhage from pulmonary infarction but maintained the perspective that "In hemoptysis the patient despairs from the first and needs to be strongly reassured. Death is rarely directly due to hemoptysis; patients die after, not of it..." (2).

Pulmonary embolism remains a major health problem. It has been estimated that 600,000 cases of pulmonary embolism occur each year in the United States causing death in 100,000 patients and contributing to death in another 100,000 patients (3). Estimates based on autopsy studies suggest that 40% to 60% of patients who have pulmonary emboli are undiagnosed prior to death (3,4). Full dose anticoagulation with heparin, and thrombolytic agents are both efficacious therapies for pulmonary emboli (3,5-7). Correctly diagnosed and treated patients have a mortality of approximately 8%. However, in untreated patients the mortality has been as high as 30% (3,5-7). Major hemorrhagic complications have occurred in 10% to 15% of patients receiving anticoagulant drugs with higher rates in elderly patients (8-10). In 1977 Porter and Jick (11) reported from the Boston Collaborative Drug Surveillance Program that heparin was the fifth most commonly implicated drug in drug-related deaths. The authors noted for other drugs that, "...those patients who died...were very ill prior to the event...," while, "Heparin continues to be the drug responsible for a majority of drug deaths in patients who are reasonably healthy."

Accurate diagnosis is thus essential not only to prevent excessive mortality from pulmonary embolism but also to avoid unnecessary complications of treatment with anticoagulant drugs in patients who do not have pulmonary embolism. Clinical signs, symptoms, chest X rays and routine laboratory findings have been reported not to be conclusive, particularly in patients with cardiac or pulmonary disease (12-14). Lung scanning is widely used in

the differential diagnosis of patients with suspected pulmonary embolism. The value and limitations of lung scanning for the diagnosis of pulmonary embolism, however, have not been adequately assessed.

1.3 NUCLEAR MEDICINE, ANGIOGRAPHY AND INTERNAL MEDICINE

Current data suggest that perfusion lung scanning has high sensitivity but limited specificity for pulmonary embolism. Normal perfusion lung scans are widely interpreted as excluding the diagnosis of pulmonary embolism although the data for this assumption are limited (15-18). Combined-ventilation-perfusion ($\dot{V}/\dot{Q}$) lung scanning improves the specificity for diagnosis of pulmonary emboli (19-22). Several studies have explored the ability of $\dot{V}/\dot{Q}$ scans to classify patients according to probability of angiographically-proven pulmonary emboli (19-25). Patients clinically suspected of having pulmonary emboli who demonstrated multiple large (segmental or greater) perfusion defects with normal ventilation have been reported to have a high probability (greater than 85%) of having angiographically documented pulmonary emboli. However, the percentage of patients with angiographically documented pulmonary emboli who had "high probability" $\dot{V}/\dot{Q}$ scans has ranged from only 32% (23) to 55% (22) in reported series. Controversy exists over the probabilities of pulmonary emboli in patients with "indeterminant" scans (matched perfusion defects and radiographic abnormalities) and in those with "low probability" scans (nonsegmental or subsegmental $\dot{V}/\dot{Q}$ mismatches or larger matches). The reported probability of pulmonary emboli in patients with nonsegmental or subsegmental $\dot{V}/\dot{Q}$ mismatches has varied from 0% (24) to 50% (25). The reported probability of pulmonary embolism in patients with nonsegmental or subsegmental $\dot{V}/\dot{Q}$ matched defects has varied from 0% (23) to 13% (25). Differences in probabilities may be due in part to different study design (retrospective versus prospective), patient selection bias, variability in scan interpretation, and small numbers in individual scan classifications. Because patients with normal, and low probability $\dot{V}/\dot{Q}$ scans have not been routinely studied with pulmonary angiography, calculation of sensitivity and specificity of lung scanning has not been possible. Interpretation of results has often led to the pitfall of generalizations based on predictive value for positive $\dot{V}/\dot{Q}$ scans (see Section 1.4).

Pulmonary angiography is the most specific test currently available for the pre-mortem diagnosis of pulmonary emboli. Specificity has been unquestioned when only intraluminal filling defects are accepted as diagnostic of pulmonary emboli (26-30).

The sensitivity of pulmonary angiography has been questioned. Hull et al have reported normal pulmonary angiograms in 33% of patients who had abnormal perfusion scans and deep vein thrombosis confirmed by leg venography (25). Whether these perfusion defects represented other lung disease, emboli that had lysed prior to angiography, or emboli missed by angiography is unknown. Autopsy studies have found 27% to 60% of autopsy cases to have deep vein thrombosis (31). The coincidence of deep vein thrombosis on leg venography and an abnormal $\dot{V}/\dot{Q}$ scan need not establish a diagnosis of pulmonary embolism. On the other hand, a negative lower extremity venogram will not exclude venous thromboembolism. The frequency of a negative venogram associated with angiographically proven pulmonary embolism was 30% in the study by Hull et al (25).

Others believe the sensitivity of careful pulmonary angiography for detection for pulmonary emboli is high. In a series of experiments on dogs,

Alderson et al showed that selective pulmonary angiography could identify all emboli greater than one mm in size (32). Bookstein et al used sub-selective, scan guided, magnification angiography. These investigators demonstrated the embolic cause of every experimentally created pulmonary embolic perfusion defect seen on scan (33). Using sub-selective, scan guided, magnification angiography, none of the 167 patients in Novelline's series with pulmonary angiograms negative for untreated pulmonary embolism died as a result of pulmonary emboli during their acute illnesses or suffered clinically suspected recurrent pulmonary emboli during the follow-up (minimum of six months) (29). Of 20 patients who died within six months of pulmonary angiography, ten had autopsies. In three autopsies, pulmonary emboli were found, but the authors had no way of knowing whether or not these emboli had been present at the time of pulmonary angiography.

Some $\dot{V}/\dot{Q}$ scan evaluation studies have been prospective (13,17,29). Other studies have allowed quantitative estimates of sensitivity (12,27). Still others have allowed quantitative estimates of both sensitivity and specificity (16,19-24), but not been prospective. No studies have both been prospective and been designed for unbiased estimates of both sensitivity and specificity.

1.4 BIOSTATISTICS

Sensitivity and specificity are critical parameters in evaluating diagnostic tests with dichotomous outcomes. Yerushalmy first rigorously presented sensitivity and specificity to the medical community as tools for analyzing deficiencies in chest X ray screening programs for pulmonary tuberculosis (34). Since then sensitivity and specificity have seen wide application in clinical medicine (35).

A two-by-two (four-fold) table relates test results to disease status in standard format.

Exhibit 1-1

Test Results and Disease Status

		Disease		
		Present	Absent	
Test Result	Positive	A	B	A + B
	Negative	C	D	C + D
		A + C	B + D	A + B + C + D = N

This table cross-classifies all individuals, A + C with disease and B + D without disease, into categories of those who test positive for disease with the disease present (true positives, "A" in number), test positive for disease with disease absent (false positives, "B" in number), test negative for disease with disease present (false negatives, "C" in number), and test negative for disease

with disease absent (true negatives, "D" in number). The algebraic definition of sensitivity is A/(A + C) and of specificity is D/(B + D).

A test's sensitivity will range from 0%, indicating complete insensitivity to or inability to mark positive those with disease, to 100%, indicating complete sensitivity to or ability to mark positive those with disease. A test's specificity will also range from 0%, indicating inability to specify or inability to mark negative those without disease, to 100%, indicating complete ability to specify or ability to mark negative those without disease. The mathematical definitions correspond pleasingly to common usage.

In vernacular English, the more attuned a test is to disease in patients with the disease of interest, the more sensitive it is. The more resistant a test is to misleading suggestions of disease in patients without the disease of interest, the more specific it is.

In rigorous mathematical terms both sensitivity and specificity are parameters of binomial distributions (36). The assumptions underlying the examination of binomial parameters are:

1. The independence of observations used to estimate the parameters.

2. Constancy of parameter from observation to observation.

3. Dichotomous outcomes possible only.

4. A finite number of observations made.

Assumptions 1, 2 and 3 are deceptively simple sounding. Assumption 4 is well tailored to medical practice because no clinician carries the burden of infinite observations.

The first three of these assumptions have profound implications for study design in the evaluation of $\dot{V}/\dot{Q}$ scans and pulmonary angiography in patients suspected of having pumonary embolism. First, the independent observations requirement demands that individual patients be eligible for the study, not individual episodes within a given patient.

Second, constancy of parameters from observation to observation demands that subgroups be analyzed to determine whether or not the diagnostic tests apply to them in the same way. Distinct subgroups of patients in whom the scanning procedures produce different results from the overall study population ought to be considered separately and not pooled into final analyses with the remaining study subjects. This information will be of key clinical value for it will help identify those patients in whom scanning techniques are especially useful and those in whom they are not.

Third, the acceptance of dichotomous outcomes only -- pulmonary embolism present or absent, tests positive or negative -- at one and the same time presents a point of clinical relevance and of analytic degeneracy. The presence and absence of pulmonary embolism are not known with finality except with the exhaustive and destructive examination of the pulmonary vasculature -- an examination unthinkable in the design of this study and in clinical practice. As a realistic compromise, the pulmonary angiogram serves as the standard of diagnosis in clinical pulmonary embolism. Moreover, the interpretation of $\dot{V}/\dot{Q}$

scans in clinical practice is not limited to pulmonary embolism present or absent. The interpreting physician may offer an opinion couched in term of probability -- high, intermediate or low -- for the diagnosis of pulmonary embolism. However, the treating physician almost always ends up deciding dichotomously to treat with anticoagulants or not to treat with anticoagulants. Provided that data are retrieved to make study $\dot{V}/\dot{Q}$ scan interpretations comparable to an exacting clinical standard, that the dichotomous outcomes are not the only ones analyzed and that follow-up allows some further scrutiny of the angiography standard for the diagnosis of pulmonary embolism -- the dichotomous outcomes are not hard to accept.

However, there is a potential design, performance and analysis error in the study. The pitfall lies in the reliance upon predictive values instead of sensitivity and specificity to assess diagnostic procedures. This fundamental error in epidemiologic science must be guarded against. It's dangers have been long documented in the medical literature (37).

A hypothetical example will highlight this problem. Suppose a diagnostic test with 95% sensitivity and 90% specificity existed. This test would be more sensitive and specific than most in clinical use.

Suppose then that this test were applied to a referral practice of 10,000 individuals of whom 20% truly had the disease of interest.

10,000 patients X 20% disease prevalence = 2,000 cases.

2,000 cases X 95% sensitivity = 1,900 true positives.

2,000 cases - 1,900 true positives = 100 false negatives.

10,000 patients - 2,000 cases = 8,000 unaffected patients.

8,000 unaffected patients X 90% specificity = 7,200 true negatives.

8,000 unaffected patients - 7,200 true negatives = 800 false positives.

In a two-by-two contingency table with margins the data are as follows:

Exhibit 1-2

Positive Predictive Values of High Prevalence Conditions

		Disease		
		Present	Absent	
Test Result	Positive	1,900	800	2,700
	Negative	100	7,200	7,300
		2,000	8,000	10,000

In this example the positive predictive value (the proportion of test positive individuals who have disease) is 1,900/2,700 = 70.4%.

Now consider that this same test (with the same sensitivity and specificity could be applied to a less highly diseased practice, say 10,000 patients presenting for routine care under a health maintenance organization (HMO) of whom only 2% have the disease of interest.

10,000 patients X 2% disease prevalence = 200 cases.

200 cases X 95% sensitivity = 190 true positives.

200 cases - 190 positives = 10 false negatives.

10,000 patients - 200 cases = 9,800 unaffected patients.

9,800 unaffected patients X 90% specificity = 8,820 true negatives.

9,800 unaffected patients - 8,820 true negatives = 980 false positives.

In a two-by-two contigency table with margins the data are as follows:

Exhibit 1-3

Positive Predictive Values of Low Prevalance Conditions

		Disease		
		Present	Absent	
Test Result	Positive	190	980	1,170
	Negative	10	8820	8,830
		200	9800	10,000

By contrast in this example, the positive predictive value (the proportion of test positive individuals who have the disease) is 190/1,170 = 16.2%.

The lesson from biostatistics is that sensitivity and specificity are not dependent upon disease prevalence in the population studied. However, the positive predictive value is highly dependent upon the disease prevalence in the population studied. A higher proportion of $\dot{V}/\dot{Q}$ scan positive individuals will have pulmonary embolism in a population with a high prevalence of pulmonary embolism than in a population with a low prevalence of pulmonary embolism. Investigators must scrupulously avoid the analytic pitfall of deciding the worth of $\dot{V}/\dot{Q}$ scans by what proportion of positive scans turn up positive angiograms.

Sophisticated statistical methods can extrapolate incidence and prevalence from less than perfect sensitivity and specificity data (38). Predictive values, however, are not transferrable across populations.

Predictive values are the clinician's decision guide, but they vary with prevalence as well as sensitivity and specificity. The clinician in his or her own practice cannot directly apply the predictive values found in a study like this one. However, with an idea of the sensitivity and specificity of the study diagnostic procedures, clinicians will be able to use clinical experience to extrapolate to his or her own practice. Without an estimate of the sensitivity and specificity of the study diagnostic procedures, clinicians could not even grope towards a sense of a procedure's predictive value in any given practice.

1.5 PROSPECTIVE DESIGN

When an important controversy has matured to the point of well defined, adversary opinions in medical science, prospective studies may be the only way to resolve differences. The prospective study is especially important in those controversies where the strongly held opinions are based on retrospective studies, case series or clinical experiences which collected data in an unsystematic way. In the diagnosis of pulmonary embolism, the design issues at the root of controversy take on added importance from the cost, mortality and morbidity associated with errors resulting from clinical uncertainties. A clinical prospective study should start with a defined population of patients at their presentation with the disease of interest; observe these patients uniformly over the whole population or in properly selected samples for baseline characteristics and later results; and then draw conclusions for the study population. This study will be a Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED).

For PIOPED prospective design has the advantages of unbiased and complete ascertainment of patient characteristics and outcome. The PIOPED investigators will have control over criteria and procedures for clinical evaluation, $\dot{V}/\dot{Q}$ scanning and angiography. The following examples clarify the importance of these advantages and emphasize their relevance to PIOPED.

First, biased patient selection presents a problem which prospective design solves. In 1929 Pearl reported on 816 autopsied cancer cases and 816 autopsied controls matched for age, race, sex and date of autopsy at the Johns Hopkins Hospital (39). He found 16.3% of the control group showed active tuberculous lesions while 6.6% of the cancer group showed tuberculous lesions. This retrospective study failed to define and enumerate the parent population for these Johns Hopkins Hospital autopsies, failed to ascertain patient characteristics of the parent populations, and failed to control criteria and procedures for evaluation in the parent population. Pearl's hypothesis that tuberculosis protected patients from cancer has not held up in further studies. The fallacies in Pearl's work are now widely recognized (40). If PIOPED were to be a retrospective study of patients who had been scanned and angiogrammed, the PIOPED investigators could be misled to any values of sensitivity and specificity of $\dot{V}/\dot{Q}$ scans should patients be analyzed only if autopsied. Autopsies could be selected either to "prove" $\dot{V}/\dot{Q}$ scans correct in the face of an opposing angiogram or to justify therapy in the face of a complication, or for any other unpredictable reason.

Second, incomplete ascertainment presents a problem which prospective design solves. In 1955 Neyman presented the consequences of incomplete ascertainment in hypothetical terms (41). PIOPED would face a problem if of 100 patients suspected of suffering from pulmonary emboli, 50 did not receive

angiograms, 25 with $\dot{V}/\dot{Q}$ scan evidence strongly against pulmonary embolism and no pulmonary embolism and 25 patients with $\dot{V}/\dot{Q}$ scan evidence strongly in favor of pulmonary embolism and pulmonary embolism present. Assuming $\dot{V}/\dot{Q}$ scan sensitivity = 0.90 and specificity = 0.80, the truth for all 100 patients could be laid out in a 2 x 2 table as

Exhibit 1-4

Complete Ascertainment with $\dot{V}/\dot{Q}$ Scans

		Angiogram	
		Positive	Negative
$\dot{V}/\dot{Q}$ Scan	Abnormal	45	10
	Normal	5	40
	Total	50	50

After 50 incomplete studies ($\dot{V}/\dot{Q}$ scans but no angiograms), the observed diagnostic studies could be laid out in a 2 x 2 table as

Exhibit 1-5

Incomplete Ascertainment with $\dot{V}/\dot{Q}$ Scans

		Angiogram	
		Positive	Negative
$\dot{V}/\dot{Q}$ Scan	Abnormal	20	10
	Normal	5	15
	Total	25	25

The excluded cases bias the estimated sensitivity and specificity for the "retrospectively" calculated sensitivity = 0.80, and specificity = 0.60. The erroneous sensitivity and specificity come of the honest clinical practice of selective ordering of diagnostic tests and the poor research practice of incomplete enumeration and ascertainment.

Third, nonuniformity of diagnostic criteria presents a problem which prospective design solves. In 1975 Siperstein published a review on diabetes mellitus, and the pitfall of varying diagnostic criteria based on different glucose tolerance tests (42). The inability to enforce uniform procedures and definitions thwarted much of the work Siperstein cited on the value of "tight" control of blood glucose in diabetics. Uniform criteria for performing both $\dot{V}/\dot{Q}$ scans and angiograms are essential to estimate summary parameters such as sensitivity and specificity for a multicenter study. Consider two hospitals,

one with very sensitive but not very specific procedures for $\dot{V}/\dot{Q}$ scan performance and interpretation and the other with very specific but not very sensitive procedures for $\dot{V}/\dot{Q}$ scan performance and interpretation. Their results could look like:

Exhibit 1-6

Nonuniform Diagnostic Criteria

Hospital 1
Angiography

Scan	Positive	Negative
Abnormal	90	40
Normal	10	60
Total	100	100

Sensitivity = 0.90
Specificity = 0.60

Hospital 2
Angiography

Scan	Positive	Negative
Abnormal	50	10
Normal	50	90
Total	100	100

Sensitivity = 0.50
Specificity = 0.90

Hospitals 1 & 2 Combined

Angiography

Scan	Positive	Negative
Abnormal	140	50
Normal	60	150
Total	200	200

Sensitivity = 0.70
Specificity = 0.75

The overall results do not reflect the truth of either diagnostic procedure. The small numbers of patients studied in each hospital will not return the narrow confidence intervals which are the fruit of the large numbers of patients in multicenter studies.

Fourth, bias from recording measurements of interest after outcome is known presents a problem which prospective design solves. In 1975 Karlowski et al reported an example of bias resulting from unblinding of treatment assignment (43,44). This bias is not always introduced consciously, and has not always been avoided in prospective studies. However, with standardized data collection procedures a prospective study has a better chance of avoiding this bias than a retrospective study which may not have had any standardized data collection procedures. In PIOPED blinding of clinical scientists to $\dot{V}/\dot{Q}$ scan and angiogram results is especially important. A pulse measured with examiner knowledge of $\dot{V}/\dot{Q}$ scan and angiogram results will be hard to establish as unaffected by the $\dot{V}/\dot{Q}$ scan and angiogram. A pulse measured before $\dot{V}/\dot{Q}$ scan and angiogram cannot be influenced by knowledge of results.

Prospective study design allows investigators to lay before the scientific community the full mechanics of patient selection and diagnostic study. Such open presentation lends study results a clarity which retrospective studies are unable to muster in the face of controversy.

1.6 SUMMARY

PIOPED seeks to answer major questions regarding the diagnosis of pulmonary embolism. Randomly sampled patients suspected of having pulmonary emboli by their primary physicians will be evaluated by the clinical scientists with a detailed history, physical examination, and review of pertinent laboratory studies. If pulmonary embolism is a diagnostic consideration, informed consent will be obtained for entering the study protocol and an estimate of the probability of pulmonary embolism will be assigned based on clinical data. $\dot{V}/\dot{Q}$ scanning will then be performed. If there is any abnormality on the scan, the patient will undergo pulmonary angiography for definitive diagnosis of pulmonary embolism. All patients will be followed closely in the hospital. There will also be systematic outpatient follow-up for a period of one year. The study design will permit the calculation of sensitivity and specificity of $\dot{V}/\dot{Q}$ lung scanning for the diagnosis of pulmonary embolism. In addition, the clinical and laboratory data, the prior probability assessment of pulmonary embolism by the clinician, and the $\dot{V}/\dot{Q}$ scan interpretation will be compared to results of pulmonary angiography.

This data base, including the derived sensitivity and specificity, will be used to construct algorithms applicable in the diagnosis of pulmonary embolism. Thus, the PIOPED results will be useful for comparing currently available and newly developed diagnostic methods for pulmonary embolism in diverse clinical subgroups. Chapter 2 will present the PIOPED design plans to meet the challenging problems in estimating the sensitivity and specificity of $\dot{V}/\dot{Q}$ scans in the diagnosis of pulmonary embolism.

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EXHIBIT 2-1
CHART OF PATIENT DISPOSITION IN PIOPED

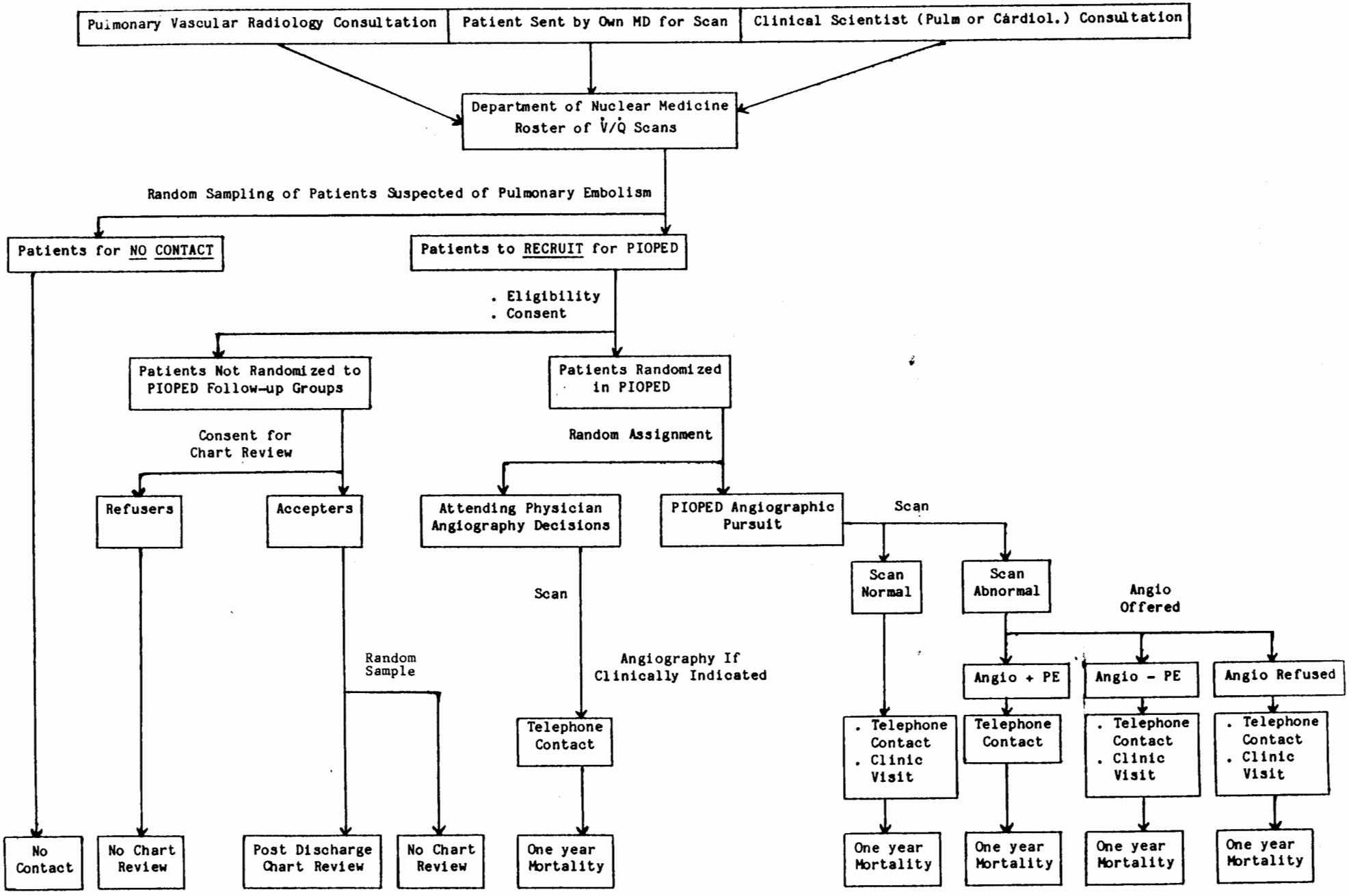

EXHIBIT 2-2

STUDY TIMETABLE

Phase	Event	Date
Phase I	Clinical Center and Data Coordinating Center Contracts Start	September 30, 1983
	First Steering Committee Meeting	November 7, 1983
	Second Steering Committee Meeting	December 5-6, 1983
	Third Steering Committee Meeting	January 16-17, 1984
	Fourth Steering Committee Meeting	February 6-7, 1984
	Fifth Steering Committee Meeting	March 5, 1984
	Sixth Steering Committee Meeting	March 30, 1984
	External Protocol Review	April 25, 1984
	NHLBI Council Review	May 18, 1984
Phase II	Patient Recruitment Starts	~~September 30,~~ January 1, 1985
	Patient Recruitment Ends	September 29, 1986
	Follow-up Ends	September 29, 1987
Phase III	Analysis Ends	September 29, 1988

CHAPTER 3

PATIENT ELIGIBILITY

3.1 CATCHMENT POPULATION

The catchment population will include all adult (18 years of age or older) patients referred for a $\dot{V}/\dot{Q}$ scan for acute pulmonary embolism or referred for consultation because of a clinical suspicion of acute pulmonary embolism. Referrals may be from any source including the outpatient clinics, emergency room, and inpatient units. There will be no effort to emphasize or reject subpopulations of patients who may pose particularly troublesome diagnostic problems.

Every effort will be made to complete the clinical scientist's evaluation before the $\dot{V}/\dot{Q}$ scan. Instances when clinical evaluation follows $\dot{V}/\dot{Q}$ scan are expected to be rare. In those few instances when the $\dot{V}/\dot{Q}$ scan is completed first, the clinical scientist will be blinded to the results of the $\dot{V}/\dot{Q}$ scan until after his clinical evaluation is completed. Deviation from the recommended order of clinical evaluation and $\dot{V}/\dot{Q}$ scanning will be noted for quality control and for analysis.

3.2 ELIGIBILITY CRITERIA

3.2.1 Entry Criteria

The clinical scientist's judgment that full evaluation for acute pulmonary embolism is warranted will be based on the occurrence of predisposing factors, symptoms, signs, presentations, or laboratory findings. Symptoms, signs, presentations and laboratory findings must be unexplained and acute. In order to recruit patients with pulmonary emboli fresh for diagnosis in PIOPED, study patients' eligibility will depend upon one or more of those unexplained and acute findings being present during the 24 hours prior to the PIOPED $\dot{V}/\dot{Q}$ scan.

a. symptoms - dyspnea, pleuritic or nonpleuritic chest pain, and hemoptysis;

b. signs - tachypnea, tachycardia, pleural friction rub, and cyanosis;

c. presentations - shock, syncope, pulmonary edema, bronchospasm, deep vein thrombosis, and right ventricular failure; and

d. laboratory findings - abnormal chest roentgenogram suggestive of pulmonary embolism, e.g., pleural effusion, suggested infarction, etc., acute electrocardiographic changes especially those suggesting right heart involvement or unexplained arrhythmia, unexplained low grade pulmonary hypertension, and hypoxemia or a widened alveolar-arterial oxygen gradient while breathing air (> 20 mm Hg).

Predisposing factors include use of oral contraceptives, congestive heart failure, recent immobilization, clinical thrombophlebitis, trauma including surgery of lower extremity or pelvis, history of thromboembolism, widespread carcinoma, dehydration, obesity, and other suspected causes of pulmonary embolism.

As it is, this study's aim is to include as broad a spectrum of pulmonary embolism presentations as possible, these criteria guide the clinical scientist to recognize clinical diagnoses of some merit. These criteria are not an algorithm for selection.

3.2.2 Exclusion Criteria

Some patients will not be candidates for pulmonary angiography against which to compare $\dot{V}/\dot{Q}$ scans. These patients will be excluded from the pursuit to angiographic diagnosis.

1. A patient may be excluded by the overall judgment of the clinical scientist that the clinical and laboratory findings (without knowledge of the $\dot{V}/\dot{Q}$ scan) are obviously explained by an event other than acute pulmonary embolism. Two possible examples are: (i) 18 year old kicked in chest playing "touch" football comes immediately to emergency room because of pleuritic pain and hemoptysis; and (ii) 56 year old male three pack a day smoker with electrocardiographically documented myocardial ischemia arrives in the ER within six hours of severe oppressive substernal chest pain radiating down the left arm, diaphoresis, dyspnea, and tachycardia, and the electrocardiogram shows new Q waves, S-T elevations and peaked T waves in AVL, V_2, and V_3. It is expected that exclusions will be extremely rare.

2. Lack of consent of patient or patient's physician.

3. Presence of medical exclusions that in the judgment of the clinical scientist or angiographer preclude evaluation, e.g., dye allergy, hemodynamic instability, pregnancy, pulmonary hypertension.

Consenting excluded patients will be followed to insure that exclusions do not seriously bias sensitivity and specificity estimations.

CHAPTER 4

RANDOM SAMPLING

4.1 RATIONALE FOR RANDOM SAMPLING

The study intends to recruit 75 patients for PIOPED angiography each year for two years from each of six Clinical Centers for a total of 900 angiogrammed patients. In all the institutions the available patient population for study is larger than that necessary to meet the quota. Thus, a random sampling procedure is necessary to make the patients studied as nearly representative of the eligible population as possible.

4.2 IMPLEMENTATION OF RANDOM SAMPLING AND ASSIGNMENT

The random sampling will be performed in the Departments of Nuclear Medicine at the time of the request for the $\dot{V}/\dot{Q}$ scan. The responsible individual will open the top numbered envelope from the stack provided by the Data and Coordinating Center. In the event of simultaneous arrival of two requisitions or requests for $\dot{V}/\dot{Q}$ scans, the exact time of arrival of the requests and their simultaneity will be documented and then study envelopes will be assigned to the patients in the alphabetic order of their surnames. These envelopes will be numbered to match Data and Coordinating Center provided patient rosters.

The envelopes will contain a sealed mailer. On the outside of the sealed mailer will be an instruction either to RECRUIT or make NO CONTACT with this patient. Inside the sealed mailer is the instruction to manage the patient for PIOPED Angiographic Pursuit or according to Attending Physician Angiography Decisions. The mailer is opened only after having established patient eligibility, having notified and secured permission from the patient's attending physician, and having obtained written informed consent from the patient.

Exhibit 4-1 presents the sampling fractions that will be followed initially to secure patients for PIOPED angiographic pursuit at the various Clinical Centers. Sampling fractions are based on each Clinical Center's number of $\dot{V}/\dot{Q}$ scans in 1982. The Data and Coordinating Center will monitor patient entry every two weeks in order to determine whether or not a change in the sampling fraction is needed at any Clinical Center in order to help it to perform 75 PIOPED angiographies per year. Clinical Centers which fall behind or run ahead of their recruitment quotas (6 patients/month) for pursuit to angiographic diagnosis, will have their sampling fractions adjusted monthly on the basis of the previous month's recruiting experience. Exhibit 4-1 also displays the derivation of sampling fractions with which PIOPED will start selecting patients for pursuit to angiographic diagnosis. Where possible, a sample equal in size to that selected for pursuit to angiographic diagnosis will be selected for attending physician angiography decisions.

EXHIBIT 4-1

RANDOM SAMPLING

	1982 Scans Performed	Number of Abnormal Scans Estimated for the First Year of Patient Recruitment	Sampling Fraction To Get 75 Angiograms	Sampling Fraction Adjusted to Accommodate a 25% Refusal Rate	Adjusted Sampling Fraction Expressed Approximately as a Crude Fraction
Duke	750	675	11%	15%	1 of 7
Henry Ford	302	272	28%	37%	1 of 3
Michigan	204	184	41%	54%	1 of 2
Yale	418	376	20%	26%	1 of 4
Mass. General Hospital	524	472	16%	21%	1 of 5
Univ. of Penn.	410	369	20%	27%	1 of 4

LEGEND:

The first column contains the number of $\dot{V}/\dot{Q}$ scans performed in 1982 in each Clinical Center. The second column contains the number of $\dot{V}/\dot{Q}$ scans abnormal by PIOPED study definitions, expected in the first year of patient recruitment. The third column contains the approximate percentage of patients with abnormal $\dot{V}/\dot{Q}$ scans who will have to be recruited to meet the study quota of 75. The fourth column represents the percentage of patients with abnormal $\dot{V}/\dot{Q}$ scans who will have to be entered based on an assumed 25% refusal rate. The fifth column is the sampling fraction for each institution based on the percentage shown in the fourth column and expressed as an approximate, crude fraction.

CHAPTER 5

PATIENT INFORMATION AND CONSENT

5.1 INTRODUCTION

PIOPED will use two consent forms. The first will be for patients entering the randomized study. The second form is to be used for obtaining consent to review charts for patients who either refuse the randomized study or who are ineligible for the randomized study (see Chapter 2).

5.2 CONSENT FOR PATIENTS SELECTED FOR PURSUIT TO ANGIOGRAPHIC DIAGNOSIS

5.2.1 Information for Consent

The following items are considered to be essential to informed consent to be obtained from patients entering the randomized study. Some institutions may require additional information on the consent form but all consent forms will address as a minimum the following items in readily understood terms.

1. A statement of the purpose of the study.
2. An explanation of the procedures involved.
3. A statement as to whether hospitalization is required.
4. A statement concerning costs, if any, to subject.
5. A description of the discomforts.
6. A description of risks, including side effects, radiation exposure, etc.
7. A special presentation of risks and benefits to the responsible individual when patients are not competent to give consent.
8. A statement of the potential benefit to the subject, others, and/or general medical knowledge.
9. A description of possible alternative procedures, if any, for the patient.
10. A statement concerning the methods of protecting confidentiality.
11. The name and telephone number of a contact person associated with the study.
12. A statement that the subject (or, if appropriate, the next of kin or the legally authorized representative):
    a. has had, and will continue to have, opportunities to obtain information about the study,

b. may refuse to participate, or may withdraw consent and discontinue participation in the study without prejudice to present or future medical care, and

c. will receive a copy of the consent form.

13. A statement concerning care in the event of injury.

14. A statement regarding follow-up information to be obtained.

15. A statement regarding requests to participate in further research.

These items are covered in the consent form in Appendix V.

5.2.2 Assessment of Risks

5.2.2.1 Radiation Risks

The information used to assess the radiation risks a patient would be exposed to while participating in this study are presented in Appendix IV. The FDA annual limit for radionuclide isotope research dose to whole body, active blood forming organs, lens of the eye and gonads is 15 REM which is the same as 15 RAD for X rays and beta emissions (1). The radiation doses received by subjects in this study are within the FDA annual exposure limit for research purposes only.

5.2.2.2 Non Radiation Risks of Pulmonary Angiogram (2)

Mortality = 0 - 0.4%
Morbidity = 4 - 8%

5.2.2.3 Risk of Not Treating Pulmonary Embolism

A. Randomized controlled study = 26% death, 39% recurrence (3).

B. Nonrandomized or uncontrolled studies = 18 to 32% mortality (4,5).

5.2.2.4 Risk of Anticoagulation (2)

Morbidity = 30%
Mortality = 4%

5.3 CONSENT FOR CHART REVIEW

The second consent form is more limited in scope as it seeks permission to passively review medical charts. Except for elimination of the detailed discussion of pulmonary embolism and pulmonary angiography, it is similar to the first form and guarantees all the same patient rights. It is attached in Appendix V.

REFERENCES

1. FDA Regulations, 1975. Title 2-L Part 361. Code of Federal Regulations, Effective July 25, 1975.

2. Cheely, R., McCartney, W.H., Perry, J.R., et al: The role of noninvasive tests versus pulmonary angiography in the diagnosis of pulmonary embolism. Am J Med 70:17, 1981.

3. Barritt, D.W. and Jordan, S.C.: Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial. Lancet 1:1309, 1960.

4. Barker, N.W., Nygaard, K.K., Walters, W., and Priestly, J.T.: A statistical study of post-operative venous thrombosis and pulmonary embolism. II. Predisposing factors. Mayo Clin Proc 16:1, 1941.

5. Zilliacus, H: On the specific treatment of thrombosis and pulmonary embolism with anticoagulants, with particular reference to post-thrombotic sequelae. Acta Medica Scandinavia Supplement (171):1, 1946.

CHAPTER 6

CLINICAL SCIENTIST EVALUATION

6.1 INTRODUCTION

Patients entering this study will be evaluated and followed by a clinical team headed by the clinical scientist. The clinical scientist, one of the Principal or Co-Principal Investigators at each center, will be responsible for the accuracy and completeness of all clinical evaluations. The purpose of this evaluation is to identify and record clinical observations which may bear on the accuracy of diagnosis of pulmonary embolism. In addition, the clinical team will prospectively follow patients enrolled in this study.

6.2 PERSONNEL

The clinical scientist will be assisted by a variety of personnel. First, each clinical scientist will appoint an alternate physician of comparable expertise who will substitute for the clinical scientist when he is absent from the hospital center. Second, the clinical scientist will also designate one or more fellows who will be immediately available 24 hours a day for recruitment, enrollment, and evaluation of all patients who are candidates for this study. These fellows (hereafter termed "designates") will be board certified or eligible internists who are engaged in full-time training in pulmonary disease. Finally, the clinical scientist will be assisted by a clinical coordinator who will maintain close contact with patients throughout the study. The special roles of these medical personnel will be described in detail below.

6.3 PATIENT ELIGIBILITY AND ENTRY

All adult patients who are suspected of having acute pulmonary embolism will be eligible for this study. For this study "acute" means that signs or symptoms suggesting pulmonary embolism as described in Chapter 3, Patient Eligibility, must be present within 24 hours of the start of PIOPED $\dot{V}/\dot{Q}$ scan performance study entry. Entry into the study will be initiated by a request for a radionuclide lung scan. In the Department of Nuclear Medicine suite, an envelope will be selected for every candidate patient. If this envelope indicates that the patient has been randomly selected for study enrollment, the clinical scientist/designate will be immediately notified.

The clinical scientist/designate will then seek informed consent from the patient and his attending physician. The clinical scientist will also ascertain whether or not the patient has any absolute contraindications to pulmonary angiography and whether or not the suspicion of pulmonary embolism has any basis. If the patient or his physician does not consent to the study or if there are contraindications to angiography the patient will not undergo PIOPED pulmonary angiography. However, permission will be sought to review the charts of excluded patients.

6.4 HISTORY AND PHYSICAL EXAMINATION

A standardized history and physical examination will be performed by the clinical scientist/designate on every patient entered into the study. This evaluation should be conducted before the performance of the $\dot{V}/\dot{Q}$ scan; in exceptional cases it may be performed immediately after the PIOPED $\dot{V}/\dot{Q}$ scan. This Protocol calls for the clinical scientist/designate to evaluate the patient without knowledge of the $\dot{V}/\dot{Q}$ scan results. Should a patient be referred from another hospital with a scan already performed, the clinical scientist evaluating the patient must not be aware of the scan results at the time he/she evaluates the patient. The purpose of this strategy is to blind this physician to information besides history, physical and routine laboratory data. This design is expected to provide insight into clinical diagnosis of pulmonary embolism. All clinical data will be recorded on study forms for computer entry. This information will be obtained prospectively by the clinical scientist/designate and not obtained through secondary sources. The clinical scientist is responsible for the quality and uniformity of these clinical assessments.

6.5 INITIAL ROUTINE LABORATORY AND CHEST X RAY

Laboratory data commonly obtained in patients screened for pulmonary embolism will be recorded. These data include a complete blood count, clotting parameters, liver function tests, renal function studies, arterial blood gases, chest X ray and electrocardiogram.

The chest X ray will be read independently by the study's chest radiologists. The clinical scientist/designate, in consultation with a radiologists, will also perform a simplified interpretation of the chest X ray. The clinical scientist's interpretation is recorded because his "on the spot" reading is likely to influence the clinical assessment for the possibility of pulmonary embolism described in Section 6.7. The results of this reading will be recorded on a study form. The electrocardiogram will also be interpreted according to specified criteria by the clinical scientist, and the details recorded on the study form. The clinical scientist/designate is responsible for making certain that current and, where possible, comparison electrocardiograms are available for PIOPED interpretation.

6.6 FINAL STUDY ELIGIBILITY ASSESSMENT

Along with the history, physical and laboratory data recording, the clinical scientist will define the patient's eligibility for entry into the study. The patient must meet the eligibility criteria outlined in Chapter 3. If the patient fails to fulfill these criteria he will no longer be considered a candidate for angiography. However, if already randomized such patients will continue to be followed in the hospital and as an outpatient.

6.7 CLINICAL PROBABILITY ASSESSMENT

The clinical scientist will provide a subjective probability assessment of the likelihood of pulmonary embolism. The likelihood in the individual patient will be based on the results of history, physical examination and routine laboratory data before, and again after knowledge of the results of lung scan.

These clinical estimates are important since the evaluation of physician decision making is an important aspect of this investigation. A secondary objective of this multi-center study is to evaluate the clinical effectiveness of the V/Q scan and of the pulmonary angiogram in patients suspected of pulmonary embolism. Clinical effectiveness of a diagnostic test is dependent on two factors.

1. The performance of the test in isolation under ideal conditions.

2. The physician's ability to interpret and apply the information provided by the test.

Correct use of a diagnostic test for pulmonary embolism requires three steps.

1. Accurate estimation of the pre-test probability of pulmonary embolism.

2. Accurate estimation of the sensitivity and specificity of the diagnostic test being used.

3. Revision of the estimated pre-test probability of pulmonary embolism in light of the diagnostic test result.

Assessment of the physician's ability to use the result of a diagnostic test accurately thus requires three estimates by the physician.

1. The pre-test probability of pulmonary embolism.

2. The sensitivity and specificity of the test.

3. The post-test probability of pulmonary embolism.

The analysis of these estimates permits distinction of inaccurate diagnosis due to limited efficacy of the test from inaccurate diagnosis due to poor processing of the test information by the physician. This distinction is important. If the test is not efficacious, effort should be devoted to the development of improved diagnostic tests. However, an educational effort would be more appropriate to deal with the problem of poor information utilization. If there is a reasonable likelihood of pulmonary embolism being present, anticoagulant therapy may be started prior to full implementation of the diagnostic workup; this judgment will be made by the attending physician.

6.8 THE $\dot{V}/\dot{Q}$ SCAN

The $\dot{V}/\dot{Q}$ scan will be performed within a few hours of entry into the study. The clinical scientist/designate will obtain the reading of the $\dot{V}/\dot{Q}$ scan from the nuclear medicine specialist. All consenting patients with abnormal $\dot{V}/\dot{Q}$ scans selected for pursuit to angiographic diagnosis will proceed to angiography. If the lung scan is completely normal, as defined in Chapter 7, the patient will not be offered angiography unless it is ordered by the attending physician. Patients with normal $\dot{V}/\dot{Q}$ scans will be followed in exactly the same fashion as patients with normal pulmonary angiography.

6.9 PULMONARY ANGIOGRAPHY

Patients eligible for pulmonary angiography will proceed to this study within 24 hours, and preferably 12 hours, of the lung scan. The results of the angiography will be rapidly conveyed to the attending physician. From this point on, all therapeutic and diagnostic maneuvers will rest with the attending physician. Records of any angiography complications will be the responsibility of the angiography investigators. However, any of these problems will also be recorded as part of the routine hospitalization follow-up data recorded by the clinical scientist.

6.10 HOSPITALIZATION - CLINICAL COURSE

All consenting patients randomly selected for PIOPED angiographic pursuit or for attending physician angiography decisions will be followed during hospitalization. These patients fall into the following categories:

No PIOPED Angiography	PIOPED Angiography
- Normal scan	- Abnormal scan
- Refused angiography	- Normal scan (angio ordered by attending)
- Angiography contraindicated	- Assignment to attending physician angiography decisions and an angiogram is performed
- Assigment to attending physician angiography decisions and no angiogram performed	

As noted above major angiography complications will be recorded. In addition, complications of anticoagulation therapy will be noted.

Suspected new embolic events will also be recorded. The patient will not be reentered into the study if a new embolic event is suspected. In cases of

suspected new embolism, every attempt will be made to encourage the physician of record to complete a full diagnostic evaluation, including angiography. However, no routine protocol for imaging or therapy will be requested. Such requests would jeopardize recruitment in PIOPED.

At the time of discharge the patient's discharge diagnoses, medication, ambulatory status, and disposition will be recorded. The patient will be strongly encouraged to continue routine follow-up procedures as noted in Chapter 9.

6.11 FOLLOW-UP

Follow-up outcome is important for the purposes of this investigation. The follow-up will depend largely on the rapport established between the patient and the investigative personnel, particularly the clinical scientist and the clinical coordinator. Close inpatient contact with patients should improve follow-up yield.

6.12 SPECIAL PROCEDURAL PROBLEMS

There are a number of logistic problems which may arise during the clinical scientist's evaluation.

First, the initial clinical assessment and the $\dot{V}/\dot{Q}$ scan reading determine which patients will be excluded from pulmonary angiography. No patient will be rejected from pulmonary angiography unless fully evaluated by the clinical scientist or his substitute. No junior member of the clinical team can reject a patient without senior consultation and approval.

A second problem is patient withdrawal during the study. Some patients or their physicians may withdraw from the study when the results of $\dot{V}/\dot{Q}$ scanning become available. These will likely be patients with little clinical evidence of pulmonary embolism and with very low probability $\dot{V}/\dot{Q}$ scan results. Patients are entitled to decline study procedures at any time, but every effort will be made to continue to follow these patients.

A third problem relates to recurrent thromboembolic events. Ideally all such suspect patients would undergo the same evaluation as they had with the originally suspected embolic event. However, this could prove impractical and threaten patient recruitment. Also, embolic events in the same patient cannot be employed in the estimation of sensitivity and specificity for reasons enumerated in Chapter 1. Therefore, in this circumstance, the attending physician will decide the appropriate diagnostic workup. In analyzing outcome data, previously defined criteria will be established to classify the likelihood of new thromboembolic events. These likelihood categories would fall into groups such as definite pulmonary embolism, probable pulmonary embolism, unknown, and no pulmonary embolism.

A final problem is maintaining contact with the local attending physician for patient follow-up. Since all hospitals in the study are tertiary care

referral centers, the local physicians outside the hospital may not be involved in the initial phases of the patient's entry into the study. Ultimately, the local physician will have to be informed of the nature of the study and his/her full cooperation actively solicited.

6.13 QUALITY CONTROL PROCEDURES

Quality control methods will be instituted to ensure accurate measurements and standardization of measurements in the following areas of the clinical science evaluation: blood pressure measurement, respiratory rate, pulse, lung sounds, heart sounds and measurement of leg circumference. In addition, specifications for equipment to be used in the clinical science evaluation will be made to further ensure standardized measurements.

Methods of quality assurance to be established include four elements.

1. Training of personnel and standardization of methods.
2. Use of quality control tapes or models.
3. Certification and recertification procedures.
4. Use of certification numbers.

Each Clinical Center will have clinical fellows certified in each area of quality control, noting that the fellow will be available at all times to ensure the quality of pertinent measures. The clinical scientist, or a member of the clinical scientist's staff, trained by the clinical scientist in PIOPED quality control procedures, will serve as the clinical quality control supervisor/trainer. Study data is to be collected only by certified personnel.

CHAPTER 7

NUCLEAR MEDICINE

7.1 INTRODUCTION

Although perfusion scan techniques are well established and standardized at this time, some differences exist among centers regarding the ventilation study procedures. This nonuniformity is mainly due to the fact that none of the tracers used has been accepted as the agent of choice for ventilation studies. Advantages and disadvantages of different agents were discussed at length by the nuclear medicine imaging group which are outlined in Exhibit 7-1. Krypton-81m was considered suboptimal for routine ventilation studies because of the necessity of daily delivery, high costs, and because washout studies are not possible (1). Because of cost and because of the lack of firm evidence for its usefulness, 99m-Tc DTPA aerosol was eliminated as a candidate for routine use in this project (2). Xe-127, although superior to Xe-133 in certain respects (3,4), is 3-4 times as expensive as Xe-133 and is distributed by only one commercial company. Delivery is not reliable at this time. Because of these considerations, Xe-133 was chosen unanimously as the best agent overall for this project and will be used as the primary radionuclide to perform ventilation scans (5). It was recommended that Xe-127 and 99m-Tc DTPA scans be performed as ancillary studies to the main project.

7.2 VENTILATION SCAN PROTOCOL

Ventilation scan (performed before perfusion study) studies will be performed according to the following protocol:

Radiopharmaceutical:	Xe-133
Dose:	15-30 mCi
Energy Peak:	80 keV - 20% symmetric window
Position during study:	Erect, sitting or standing. (Supine or reclining if patient cannot tolerate upright position. Note position on data sheet.)
Collimator:	Parallel hole, low energy, all purpose.
Projections:	Posterior (wash in, equilibrium, 3 first washout and last washout images); both posterior obliques during washout.
Count/Time per image:	a) First breath image - 100,000 counts b) Equilibrium (wash in) images - 2 consecutive 120 sec images beginning after first breath images.

c) Washout images - 3 serial 45 sec views, followed by 45 sec right and left posterior obliques, followed by final 45 sec posterior view. (Intensity should be turned up during later phases of washout to enhance detail as the count rate decreases.)

Scintillation Camera:	Wide field of view.
Film:	Use 8 x 10 inch film, either clear or tinted base, 9 images/1 film. (If performed according to protocol this study should fit on one piece of film.)

Every attempt will be made to obtain ventilation study in patients on assisted ventilation. Incomplete studies will be used in the interpretation of scans and recorded in the data analysis form.

7.3 PERFUSION SCAN PROTOCOL

7.3.1 Technical Specifications for Perfusion Scans

Perfusion scans will be performed following the ventilation studies as follows:

Radiopharmaceutical:	Technetium 99m macroaggregated albumin (^{99m}Tc MAA)
Dose:	4 mCi
Number of Particles/Dose:	100,000 - 500,000
Energy Peak:	140 keV - 20% symmetric window
Position during Injection:	Supine (patient may be erect or reclining if they cannot lie flat - note position during injection on the data form). Inject slowly over 5-10 respiratory cycles. Do not draw blood into the syringe.
Collimator:	Parallel hole, low energy, all purpose.
Position during Imaging:	Erect, sitting or standing. (Supine if patient cannot cooperate. Note imaging position on data sheet.)
Projections:	Anterior, posterior, both laterals, both posterior obliques, both anterior obliques.

Number of Counts/Image:	750,000 for posterior, anterior and all obliques. 500,000 for lateral view with best perfusion (as seen on posterior view), same time for other lateral.
Scintillation Camera:	Wide field of view.
Film:	Use 8 x 10 inch film, either clear or tinted base, 9 images/film. (If performed according to protocol, this study should fit on a single piece of film.)

Refer to Appendix II for $\dot{V}/\dot{Q}$ data recording forms.

7.3.2 Protocol Modifications and Complications

1. Pregnant patients may be studied for clinical reasons, but will not be studied under the PIOPED protocol. If scanned, the dose should be decreased to 1 mCi, but such patients must receive at least 100,000 total particles.

2. Limit the number of particles to the minimum value, i.e., 100,000, in patients with known right-to-left shunts or elevated pulmonary arterial pressure (6,7).

3. Perform the study as tolerated by the patient. Record all deviations from strict protocol on the data sheet.

4. Patients with a history of prior mild reaction to MAA -- proceed with injection cautiously and slowly; physician should be in attendance. With a history of severe reaction (with hypotension), study will not be performed.

7.4 NUCLEAR MEDICINE QUALITY CONTROL

The following data must be collected to ensure the quality of scan studies across Clinical Centers.

1.	99m Technetium Macroaggregated albumin (99m-Tc MAA)	Vendor's name should be recorded
	(a) Particle size	10-90 micron (90-95%) No particle greater than 150 micron
	(b) Unbound 99m-Tc	Less than 5%
	(c) Maximum time between preparation and injection	6 hours

For (a) and (b), throughout the study investigators will rely on the specifications provided by the vendors. However, before the study is initiated, and several times during the study, particle size and percent unbound 99m-Tc will be checked by each center to determine the accuracy of the specifications presented by the radiopharmaceutical companies.

2. Xe-133 — No quality control of gas preparation will be performed

3. Scintillation camera

   (a) Field uniformity determination obtained daily

   Source: 99m-Tc sheet source or Cobalt-57 sheet source

   Collimator: Attached to the camera (or point source without collimator)

   Film: The same used for patient studies

   Counts/image: 10^6

   Maximum count rate: 10^4/sec

   Images should appear uniform on visual inspection.

   (b) Resolution and linearity determination (twice a week)

   Use four quadrant bar phantom (3, 3.5, 4, and 4.5 mm bar) with 99m-Tc sheet source or 57Co sheet source

   Collimator: attached to the camera

   Film: The same used for patient studies

   Counts/Image: 10^6

   4 mm bar must be resolved.

4. Film — Single emulsion, clear or tinted base

   Vendor's name should be recorded

5. Scans examined will be judged by each reviewer for their quality, completeness, and whether an interpretation can be rendered. The following criteria will be used to categorize the study:

   (a) Satisfactory/Limited — An examination that appears to be acceptable technically will be called satisfactory.

Therefore, studies with inadequate number of counts/image, improper intensity setting, motion or other artifact will be considered limited.

(b)	Complete/Incomplete	A study will be considered incomplete if all the views and phases specified in the protocol are not obtained or perfusion scan is not accompanied by a ventilation study.
(c)	Interpretable/Uninterpretable	Attempts will be made to generate an interpretation with each set of scans/chest X rays. If for any reason this goal cannot be achieved the reviewers will categorize the study as "uninterpretable." The time interval between chest X ray and scan should not exceed six hours.

All the data related to quality control should be securely maintained in the nuclear medicine laboratories and be available for inspection by the visiting consultants. (See Chapter 12).

Normal Perfusion Scan

When the injection is made in the supine position, activity is uniformly distributed throughout with slight diminution from the bases to the apices and from the posterior to the anterior aspects of the lungs. The outlines of the perfusion scans are smooth and correspond exactly to the shape of the lungs as seen on the chest X ray. The heart produces a clearly defined defect in the anterior, left lateral and both anterior oblique views. Hilar and aortic impressions may be seen as minimal perfusion defects.

If the injection is given in the erect or reclining positions, the apex to base gradient becomes more apparent. This should be taken into consideration in the interpretation of the perfusion scan.

Any perfusion pattern that differs from those described above should be considered abnormal. This includes patterns seen with cardiomegaly (any degree of enlargement), prominent and enlarged hila, prominent and enlarged aorta, widened mediastinum, and elevated diaphragms.

Normal Ventilation Study

A normal ventilation study in the posterior projection reveals uniform and symmetric activity distribution in both lungs on washin, equilibrium, and washout images. The outline of the lungs on these scans corresponds exactly to that seen on the chest X ray. When the study is performed in the supine view, no significant apex to base gradient is noted. A slight apex to base gradient is seen when the patient is examined in the erect position.

During the washout phase radioactivity is uniformly and symmetrically cleared from both lungs. In the erect position the washout rate from the bases is more rapid than that from the apices, while in the supine position both clear with the same rate. Normally all activity is cleared from the lungs by three to four minutes.

Any ventilation patterns that differ from those described above should be considered abnormal. Areas of abnormal ventilation may show less activity than the surrounding lung in all three phases of the study. Others may reveal decreased activity in the washin phase, normal activity at the end of the equilibrium phase, and slow clearance rate during the wash in phase. In some instances the area of abnormal ventilation may be detected only during the washout phase.

7.5 PROPOSED CRITERIA FOR INTERPRETATION OF $\dot{V}/\dot{Q}$ SCANS

7.5.1 Classification of Ventilation-Perfusion Defects

Definition of Segmental and Nonsegmental Defects:

A segmental defect is a perfusion abnormality that is caused by occlusion of a branch of the pulmonary arterial tree and is characterized by a triangular or rectangular shaped appearance on the perfusion scan depending upon the projection of the segment. A nonsegmental defect does not conform to segmental anatomy.

Lobar or whole lung defects will be considered in relation to their component segments, e.g., right upper lobe will be considered equivalent of three large defects.

Classification of perfusion defects:

Small subsegmental - < 25% of a pulmonary segment.

Moderate subsegmental - > 25% and < 75% of a segment.

Large (segmental) - > 75% of a segment.

The size of a nonsegmental defect will be determined in relation to the upper, middle or lower thirds of each lung region.

Ventilation scans and chest radiographs will be defined in reference to any corresponding perfusion defects by the following code:

N normal

= abnormal, same size as perfusion defect

< abnormal, smaller in size than corresponding perfusion defect

> abnormal, larger in size than corresponding perfusion defect

D abnormal, diffuse lung disease (chest radiograph only)

7.5.2 Classification of Probability for Pulmonary Embolus

The criteria described below will be used to interpret prospectively the studies obtained, and for processing at the local level for purposes of making clinical decisions.

Immediately following the completion of $\dot{V}/\dot{Q}$ scans a local interpretation of the study will be carried out and the results will be communicated to the clinician scientist, referring physician and other physicians included in the care of the patient.

Central probability interpretation of $\dot{V}/\dot{Q}$ scans will follow these criteria:

1. Normal

   a) - Pattern where the outlines of perfusion scan corresponds exactly to the shape of the lungs as seen on the chest X ray. Hilar and aortic impressions may be seen as minimal perfusion defects.

   b) - Chest X ray and/or ventilation study may be abnormal.

2. Very low probability

   a) - ~~Three or fewer~~ One to three small (< 25% of a segment) perfusion defects with a normal chest radiograph, regardless of ventilation scan.

3. Low probability

   a) - Nonsegmental perfusion defects, e.g., very small effusion causing blunting of the costophrenic angle, cardiomegaly, enlarged aorta, hila and mediastinum, and elevated diaphragm.

   b) - Single moderate subsegmental (> 25% and < 75% of a segment) perfusion defect with normal chest X ray regardless of ventilation scan findings.

   c) - Any perfusion defect with a substantially larger chest X ray abnormality regardless of ventilation scan.

   d - Matching $\dot{V}/\dot{Q}$ defects involving ≤ 50% of one lung, as long as ≤ 75% of one lung zone (upper, middle or lower) is affected. Chest X ray may appear normal or minimally abnormal in the involved areas.

e) – Multiple (more than three) small defects (<25% of a segment) are low probability irrespective of number of defects, ventilation scan findings, or chest X ray findings.

f) – One to three small perfusion defects with matching chest X ray abnormalities regardless of ventilation scan findings.

4. Intermediate probability

a) - All scans not falling in either normal, very low, low, or high probability categories will be designated as having intermediate probability for pulmonary embolism. When a study is considered "borderline high" or "borderline low", or the reviewer has difficulty categorizing it as low or high, the examination will be interpreted as intermediate.

5. High probability

a) - Two or more large (> 75% of a segment) perfusion defects without ventilation or radiographic abnormalities.

b) - Two or more large (> 75% of a segment) perfusion defects substantially larger than either matching ventilation or chest X ray abnormalities.

c) - Two or more moderate subsegmental (> 25% and < 75% of a segment) and one large (> 75% of a segment) perfusion defect without matching ventilation or chest X ray abnormalities.

d) - Four or more moderate subsegmental (> 25% and < 75% of a segment) perfusion defects without ventilation or chest X ray abnormalities.

7.6 DETERMINATION OF INTER- AND INTRA-OBSERVER VARIABILITY OF SCAN INTERPRETATIONS

The plan for interpretation of the $\dot{V}/\dot{Q}$-chest X ray is as follows.

The $\dot{V}/\dot{Q}$ scans, with the accompanying chest X rays of patients who are enrolled in the study will be copied and the original films will be mailed to the Maryland Medical Research Institute (MMRI). A certain number of these scans/chest X rays will be sent to one of the participating centers for interpretation by the nuclear medicine specialist in that institution. The same scan/chest X rays will be shipped to another center (by the first center) for similar interpretation. These centers must not have participated in generating the scans/chest X rays mailed to them. The interpretation by the nuclear medicine specialist will include only the probability rating for pul-

INDICATIONS FOR A REPEAT PERFUSION SCAN

A repeat perfusion lung scan will be performed in every patient whose inferior vena cavagram demonstrates thrombosis. Also, in patients whose angiographic findings significantly differ from those noted on the scan, a second perfusion scan will be obtained. A significant difference is defined as the presence of an isolated segmental (or larger) clot in a lobe which appears normally perfused on the scan. The repeat perfusion lung scan should be performed no sooner than 12 hours and no later than 24 hours after the completion of the first scan.

monary embolism. The scans/chest X rays will be returned to the MMRI soon after they are reviewed. Soon thereafter, two nuclear medicine investigators (not necessarily from the same two centers) will travel to the MMRI and jointly will render a detailed descriptive reading of the $\dot{V}/\dot{Q}$ scan/chest X ray findings. Interobserver variability between two nuclear medicine investigators will be determined by using only the probability rating obtained from the initial independent interpreation. If the independent probability rating differs between the two independent readings, a third nuclear medicine investigator will make an independent interpretation of the study. If two or the three readers agree, the majority interpretation will be accepted. Otherwise, the scan probability interpretation will have to be resolved by the entire nuclear medicine working group. The entire nuclear medicine working group will assemble once a year to interpret these studies and discuss some other matters related to the project. This session will preceed the Steering Committee meeting. Following the initial independent interpretation two interpretors will jointly prepare a consensus reading. This interpretation will include only the descriptive reading. These two investigators will make every effort to reach a consensus on each case. In case of disagreement, the study will be interpreted by the entire nuclear medicine working group.

Scans/chest X rays of patients who are randomized to be included in the study but refuse or are excluded for any reasons from undergoing the PIOPED protocol will be interpreted only by the local investigator using the above-described criteria. This will include the probability rating only. These scans/chest X rays will not be shipped to MMRI.

The ultimate plan is to develop new criteria for scan interpretation by correlating the consensus descriptive reading with the corresponding arteriographic interpretation. Then, these new criteria will be tested on the latter half of the data base and the results will be compared to those obtained by utilizing the criteria developed by the PIOPED investigators. The results obtained may be used in developing the new criteria for scan interpretation.

In order to determine intra-observer variability, each investigator will reread selected scans on two occasions about four months apart. Inter-observer variability will also be determined between the consultants and investigators from the participating centers. For both intra-observer variability and the latter inter-observer variability determination only the probability rating for PE will be used.

Before Phase II of this study begins, several practice sessions will be held at participating Clinical Centers. All consultants to this project and investigators from the study centers participating in nuclear medicine procedures will take part in these sessions. A large number of scans and chest X rays with different findings will be reviewed and discussed during these sessions. A uniform and accurate scheme will be determined and adopted by all involved in the analysis of the scans and chest X rays.

7.7 ROLE OF OUTSIDE CONSULTANTS

Two consultants from outside the participating centers will be recruited

by the National Institutes of Health. The consultants will visit the various Clinical Centers once a year for quality control and possibly for other duties. Each consultant will participate in the same scan/chest X ray interpretation scheme as nuclear medicine investigators involved in this study (see Section 7.6). Also consultants will participate in the yearly meeting of the Nuclear Medicine Working Group which will preceed the Steering Committee Meeting. One consultant will also be a member of the Data Monitoring Committee.

In addition, as stated in Section 7.3, nuclear medicine consultants will participate in practice sessions held at participating Clinical Centers prior to the start of Phase II.

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Exhibit 7-1

Advantages and Disadvantages of Ventilation Isotopes

	Xe-133	Xe-127	Kr-81m	99m-Tc DTPA Aerosol
OPTIMALLY PERFORMED AFTER PERFUSION SCAN	No	Yes	Yes	Yes?
PRINCIPLE PHOTON ENERGY (keV)	80	127,203	190,188	140
HALF-LIFE	5.2 days	36.4 days	13 sec.	6 hrs.
WASHOUT STUDIES MAY BE PERFORMED	Yes	Yes	No	No
DELIVERY	Weekly	Weekly-Monthly	Daily	Daily
COMMERCIALLY AVAILABLE	Yes	By one company delivery not reliable	Yes	Yes
COSTS	Low	High	Very High	Moderately High

In each patient referred for $\dot{V}/\dot{Q}$ scan, a ventilation study will be performed using Xe-133 followed by a perfusion scan with 99m-Tc MAA.

from Abass Alavi
5/30/85

INDICATIONS FOR A REPEAT PERFUSION SCAN

A repeat perfusion lung scan will be performed in every patient whose inferior vena cavagram demonstrates thrombosis. Also, in patients whose angiographic findings significantly differ from those noted on the scan, a second perfusion scan will be obtained. A significant difference is defined as the presence of a segmental (or larger) clot in an area which appears normally perfused on the scan and measures 50% or more of the affected lung area. The repeat perfusion lung scan should be performed no sooner than 12 hours and no later than 24 hours after the completion of the first scan.

CHAPTER 8

ANGIOGRAPHY

8.1 INTRODUCTION

8.1.1 Timing of Studies

Because of the possibility of lysis of some pulmonary clots, or of re-embolization, it is important that the angiographic evaluation occur relatively soon after the $\dot{V}/\dot{Q}$ scan has been completed. However, emergency angiography, particularly in patients who are not particularly ill and who have a "very low probability" scan, is difficult to justify. In general, unless urgent clinical reasons are present, angiography will be done during the daytime hours. It has been the experience of PIOPED angiographers that studies done on an emergency basis at night or early in the morning are technically inferior to those done by the regular angiographic team during the day, and that complications are more frequent and more difficult to treat at off hours. The experience of the Urokinase Streptokinase Pulmonary Embolism Trial indicates that delays less than 24 hours between the scan and the angiogram will not seriously affect the correlation between the two studies. It is expected that the majority of patients will be studied considerably earlier - within six to eight hours following the $\dot{V}/\dot{Q}$ scan. Twenty-four hours is the maximum PIOPED will tolerate. Patients who, for various reasons, cannot have an angiogram completed within 24 hours of their $\dot{V}/\dot{Q}$ scan will have to have another scan or will not be angiogrammed in the study.

8.1.2 Prerequisite Data for Angiographer

The angiographer will have available a chest X ray and the $\dot{V}/\dot{Q}$ scan. The patient's chart will be available with the ECG, preliminary evaluation of renal function, and signed consent form. The clinical scientist evaluation will also be available, and consultation with the clinical scientist will occur prior to the study.

8.2 PATIENT RECRUITMENT AND EXCLUSIONS

8.2.1 Patient Recruitment

Any adult patient suspected of having acute pulmonary embolism is a potential candidate for entering the study. The individual primarily responsible for patient recruitment will be the clinical scientist. Occasionally, however, patients will be referred directly to angiography either with or without a prior V/Q scan. Under these circumstances, the clinical scientist and nuclear medicine specialist will be notified immediately so the patient can be considered for enrollment in the study in a manner identical to all other patients.

8.2.2 Exclusions

Patients under the age of 18 and pregnant women will be excluded from PIOPED protocol angiography. Patients having other contraindications for angiography

consist of those with severe renal failure, severe shock, proven contrast aller or recent myocardial infarction. Patients with left bundle branch block (LBBB) will be considered for insertion of a right ventricular pacemaker prior to performing angiography in order to prevent asystole. It is not unlikely that, depending on clinical judgment, some patients with these contraindications will be included in the study (e.g., if indications for angiography outweigh contraindications). Other patients may have angiography but not have been selected for pursuit to angiography, and still others may not be judged suitable candidates for angiography.

8.3 TECHNICAL PROCEDURE FOR PULMONARY ANGIOGRAPHY AND INFERIOR VENACAVOGRAPHY

8.3.1 Procedural Steps

1. Procedure explained by radiologist and questions answered. Consent obtained as per practice in each participating hospital.
2. Hospital record, chest X rays and $\dot{V}/\dot{Q}$ scans reviewed.
3. Angiography procedure form (see Appendix III) initiated.
4. Patient history noted regarding allergy to contrast media.
5. ECG reviewed, especially regarding presence of LBBB.
6. Baseline systemic blood pressure, pulse rate and respiratory rate measured and recorded.
7. If there is no IV line in place, IV started through an arm vein.
8. Blood pressure cuff applied for periodic BP monitoring throughout procedure.
9. ECG leads attached to patient for continuous ECG monitoring throughout procedure.
10. Face mask applied for continuous O_2 administration throughout procedure (optional).
11. In patients with LBBB a temporary pacemaker will be inserted percutaneously via a femoral or brachial vein, and its pacing tip will be positioned at the apex of the right ventricle.

8.3.2 Venous Access

The femoral vein approach will be used in the majority of patients. If contraindicated (i.e., previous inferior vena cava ligation or interruption, groin infections, etc.), an antecubital vein approach may be used. Standard

Seldinger technique will be used to gain venous access. A multiple sideholed, pigtail catheter of 6-8 French will be advanced into the iliac vein. Small amounts of contrast (5-8 ml) will be injected by hand, and the patency of the IVC will be fluoroscopically checked, while the catheter is advanced to the right atrium. If massive thrombus is identified in the inferior vena cava, the study may be terminated or, at the discretion of the vascular radiologist, a second puncture may be made in an antecubital vein and the pulmonary vasculature approached through the arm. If no thrombus or a small amount of mural thrombus is identified, the catheterization procedure will continue as detailed below.

8.3.3 Catheterization of the Pulmonary Arteries

From the right atrium, with the aid of a deflecting guidewire, the catheter will be advanced through the pulmonary outflow into the main pulmonary artery.

8.3.3.1 Physiologic Monitoring

Continuous ECG monitoring will be carried out throughout this phase of catheterization. The induction of serious or life-threatening arrhythmias may be considered as an indication for discontinuation of the procedure at the discretion of the vascular radiologist. If no clinically significant arrhythmias occur, the catheter will be directed into the main pulmonary artery supplying the lung with the greatest $\dot{V}/\dot{Q}$ scan abnormality. Pulmonary arterial pressures (systolic, diastolic, and mean) will then be measured with fluid filled catheters and strain gauges (with the gauge placed at mid-thoracic level) and recorded on angiography forms. The study may be discontinued or modified at the discretion of the vascular radiologist if these pressures indicate the procedure will be hazardous.

In patients with recent myocardial infarction, congestive heart failure or other serious cardiac abnormalities, the right ventricular end diastolic pressure will be determined before entering the pulmonary artery. If the end diastolic pressure in the right ventricle exceeds 20 mm Hg, the study will be modified (superselective positioning of the catheter and decreased contrast injection rates) or discontinued at the discretion of the vascular radiologist. Patients with right ventricular end diastolic pressures less than 20 mm Hg will undergo the standard angiographic procedure.

8.3.4 Pulmonary Arteriography

1. Anteroposterior (AP) View. Initial filming will be in the AP projection using 14" x 14" (35.6 cm x 35.6 cm) cut film. The catheter tip will be positioned so the entire pulmonary artery supply to the relevant lung may be visualized. Seventy-six percent iodinated contrast (Renografin or Hypaque) will be injected at a rate of 20-25 ml/sec for a total of 40-50 ml (2-second injection). Filming will be carried out at a rate of 3 films/sec for three seconds, followed by one film/sec for 4-6 seconds. Depending on the size of the lungs, filming will be nonmagnification or a low magnification of 1.4x. A 12:1 ratio grid will be used, and radiographic factors will be in the range of

70-80 kVp and 0.025-0.040 seconds at 1000 mA (large focal spot of 1.2-1.5 mm diameter).

2. Magnification Oblique Views. If obvious pulmonary emboli are not identified in the AP projection, a magnification oblique view will be obtained. Selection of the specific areas to be studied will be based on the radionuclide scan abnormality or areas will be chosen that do not appear to be normal on the previously obtained angiographic series. The precise view and degree of obliquity will be determined on the basis of the previously obtained studies. In most cases, the catheter will be advanced more selectively into the lobar or segmental pulmonary arteries supplying the area in question. Depending on the degree of selectivity, the injection rate and amount of contrast material will be decreased. As on the other injection, 76% concentrated contrast will be used. The filming program may be altered, based on the fluoroscopy results of a hand injection of contrast. Generally, magnification will be 1.8-2.0x. Films will be obtained with an air-gap technique (i.e., no grid will be used). Radiographic factors will be in the range of 78-88 kVp and 0.040-0.080 seconds at 160 mA (small focal spot of 0.3-0.6 mm diameter).

3. Contralateral Lung. If no definite pulmonary emboli are identified in the lung initially examined, or, if quantification of the degree of embolization is clinically indicated, the catheter will be directed into the contralateral lung. This will be done using standard guidewire deflection techniques. Catheter position, contrast injection rates, and filming programs will be identical to those described above for the lung initially examined. More specifically, an AP view of the entire lung will be obtained, followed by a magnification oblique view of the base or of suspicious areas. To restrict radiation exposure, magnification views will be limited to 10 films.

All injections and filming sequences will be recorded as they occur, on the angiography form.

8.3.5 Catheter Removal from Pulmonary Artery

At the conclusion of contrast injections and filming, the catheter will be withdrawn to the right atrium while "pull out" pressures are measured and recorded after five minutes when all dye has cleared. These include right ventricular systolic, end diastolic and mean pressures in the pulmonary artery and right atrium.

8.3.6 Inferior Venacavography

Inferior venacavography will be performed in patients with pulmonary angiograms assessed during performance as positive for emboli.

The pigtail catheter will be withdrawn from the right atrium and the side holes positioned at the point of confluence of the right and left common iliac veins. Iodinated contrast (76% Renografin or Hypaque-diatrizoate meglumine 66%, diatrizoate sodium 10%) will be injected at a rate of 20-30 ml/sec to a total

volume of 40-50 ml. Films will be obtained in the AP projection to include the entire inferior vena cava up to the level of its juncture with the right atrium. Filming will be carried out at a rate of two films per second for a total of three seconds. Radiographic factors for an average patient are kVp of 73-75 and exposure time of 0.040-0.50 seconds at 1000 mA; these factors will be modified to account for variations in the patient's body habitus.

8.3.7 Catheter Removal

At the conclusion of the study the catheter will be removed from the femoral vein. Manual pressure will be applied to the puncture site for ten minutes following the removal of the catheter. When adequate hemostasis is obtained, the patient will be returned to the care of the referring clinicians.

8.3.8 Post-procedure Patient Care

Generally, the punctured extremity will be immobilized for a period of two to five hours to decrease the likelihood of any bleeding from the puncture site. There will also be frequent monitoring of the patient's heart rate and blood pressure, along with visual inspection of the puncture site for a period of two to four hours following study.

The reasons, if any, for pulmonary angiography modification, as well as any complications, will be listed in the angiography form (see Appendix III), and the form will be kept together with the films for subsequent review.

8.4 RATIONALE FOR PULMONARY ANGIOGRAPHIC PROCEDURE

8.4.1 Rationale for Study of Specific Lungs

In an ideal study designed to correlate the $\dot{V}/\dot{Q}$ scan with pulmonary angiography, every defect demonstrated on the scan should be studied angiographically, and all vessels in both lung fields should be carefully studied angiographically to determine whether or not emboli might be present that did not produce perfusion defects on the scan. However, a radical change in usual institutional protocols for studying embolism angiographically might seriously diminish effectiveness in recruiting patients into the study. Usual practice in three institutions involved in this study is to terminate angiography upon clear demonstration of a pulmonary embolus, and not to study both lungs in their entirety. Usual practice in three other institutions is to do more extensive angiography and to study both lungs even if the initial angiographic injection demonstrates an unquestioned embolus in one lung. The former group of institutions basically studies the patient for the presence of embolism, while the latter studies each lung for its presence. In the absence of demonstrated embolism, all hospitals study both lungs as thoroughly as possible.

For the purposes of this study, at least one lung will be studied completely, even if the initial angiographic procedure demonstrates embolism. In the presence of demonstrated embolism, study of the opposite lung is encouraged but is optional. The condition of the patient prior to angio-

graphy, and the response of the patient to angiography will also effect the completeness of the study.

8.4.2 Inferior Venacavography (IVCG) - Rationale for Including in Study

A very small percentage of patients in this series will have inferior vena cava clots. In this small group, there is a possibility that clots will be dislodged from the inferior vena cava into the lung during passage of the catheter up the inferior vena cava for pulmonary angiography. If this were to occur, there would be considerable discrepancy between the results of the pulmonary angiogram and the $\dot{V}/\dot{Q}$ scan.

In order to avoid the possibility of iatrogenically producing these discordant results, all patients in whom pulmonary emboli have been demonstrated on the pulmonary angiogram will have an inferior venacavogram (IVCG) performed upon completion of the angiogram, using the same catheter as for the pulmonary angiogram. The catheter will simply be withdrawn from the pulmonary circulation to the iliac veins and a standardized IVCG will be done. This study will be interpreted with the pulmonary angiogram on the interpretation form (see Appendix III).

A small number of patients (estimated to be 20 or fewer) are expected to demonstrate inferior vena caval clot on the ICVG. These patients will have a repeat $\dot{V}/\dot{Q}$ scan as soon as possible after the angiogram, to determine whether or not there is a significant change (for the worse) in the perfusion defects as compared to the pre-angiogram $\dot{V}/\dot{Q}$ study. Although the numbers of patients involved are likely to be small, they may be important to this study since they might indicate that the presence of inferior vena cava clot could lead to discordant angiographic-isotopic correlations.

Since approximately 150 patients with pulmonary embolism are expected to be studied, the IVCG will also provide information on the frequency of inferior vena cava clot in patients with proven pulmonary embolism.

8.5 PROTOCOL MODIFICATIONS AND RECORDING OF COMPLICATIONS

In certain instances it may be necessary to modify the angiographic procedure. Reasons for modifying a procedure are listed in the angiographic technical form in Appendix III. When, prior to the angiogram, modifications can be predicted as likely, the angiographer will consult with the clinical scientist. Modifications that could not be anticipated prior to the angiographic study will be the responsibility of the angiographer.

Complications occurring during or following the study will be recorded on the same angiographic procedure form. The form will be completed by the angiographer following the procedure and will be forwarded to the Data and Coordinating Center.

8.6 ANGIOGRAPHIC INTERPRETATION

8.6.1 Local Institutional Interpretation

The usual local institutional interpretation will be carried out immediately upon completion of the angiographic study. The clinician scientist, the referring physician, and other physicians involved in the care of the patient will be notified of the angiographic interpretation.

The pulmonary angiographic study will then be interpreted by the principal angiographer involved in this protocol and recorded on the official angiographic interpretation form (see Appendix III). Selected angiographic films will be copied for retention at the local institution.

All original pertinent angiographic films will be mailed to the Data and Coordinating Center. For each angiographic run on a patient, a film prior to injection of contrast material, and all X rays in which contrast material is seen in the pulmonary circulation will be mailed. The study angiographer's official simple interpretation (see Appendix III), and the completed angiographic procedure sheets (see Appendix III), will accompany the angiographic study.

8.6.2 Central Angiographic Interpretation

Each angiographic study will be independently interpreted by two members of PIOPED's angiographic panel. The panel will consist of the angiographers of the six institutions involved in the study. The Data and Coordinating Center will assign angiograms for interpretation so that no member of the panel performs an independent interpretation of angiograms from his own institution. The Data and Coordinating Center will send angiograms along with a copy of the $\dot{V}/\dot{Q}$ scan for detailed interpretation by a panel member at his own institution. Following completion of this interpretation, the panel member will forward the angiogram to the second assigned participating institution for a simple angiographic interpretation. After completion of the second interpretation, the angiograms and completed forms will be returned to the Data and Coordinating Center.

8.6.3 Criteria for Diagnosis of Pulmonary Embolism

The angiograms will be assessed by the paired panel readers as to whether or not pulmonary embolism is present. The first reader will also record details of location, size of embolism, and whether or not vessel obstruction is complete. Criteria for the diagnosis is restricted to two angiographic observations: a) identification of the trailing edge of a thrombus obstructing a vessel, and b) identification of an embolus outlined by contrast material in a vessel (filling defect).

8.6.4 Inter-observer Disagreement

In the event that the two independent angiographic interpretations agree with each other but disagree with the original institutional interpretation which had been forwarded to the Data and Coordinating Center, that information will be conveyed as soon as possible to the Policy and Data Safety Monitoring Board.

In the event that the two independent, central, simple angiography readings are divergent, the full angiogram will be sent to a third member of the panel for independent interpretation. If this third interpretation is in agreement with one of the two original readers' simple interpretations, that interpretation will become the official interpretation. In the event that there is disagreement among the three independent interpreters, the angiogram will be discussed at a meeting of the angiographic panel. It is anticipated that such meetings will occur two to three times each year of the study.

Disagreement between the two independent review panelists as to whether or not pulmonary embolism is present will be regarded as major disagreement and will require adjudication by a third independent observer and possibly by a meeting of the panel.

8.6.5 Intra-Observer Variation

The Data and Coordinating Center will resubmit a sample of angiographic studies for re-interpretation by observers in order to determine intra-observer disagreement. In addition, the original interpretation of the angiograms by the panel will include the $\dot{V}/\dot{Q}$ scan, since angiographic interpretation in most institutions is performed with knowledge of the results of the scan. The Data and Coordinating Center will resubmit a sample of the angiograms for reinterpretation without the scan in order to determine whether intra-observer variation is affected by the presence or absence of the scan with the angiogram at the time the latter is interpreted.

8.7 OUTSIDE CONSULTANTS

Participation of outside consultants is essential. In angiography, their role will be directed toward quality control of the technical aspects of angiography, and toward active participation in the independent interpretation of angiographic studies. It is not deemed necessary for outside consultants to interpret every angiogram, but enough studies should be independently interpreted in order to determine whether the interpretations of the regular panel members are in some way biased.

Outside consultants should visit each institution at least once yearly. At the time of the visit, problems in angiographic logistics, in quality control, and in patient handling should be assessed. In addition, since each panel member will be interpreting angiograms from other participating institutions in his own department, the outside consultant should independently

interpret a group of 10-15 angiograms during his visit. The official, simple angiographic interpretation form will be completed by the outside reviewer and will be forwarded to the Data and Coordinating Center.

The outside consultants will attend meetings of the angiographers at the Data and Coordinating Center to adjudicate difficult cases. In addition, prior to the initiation of the study, the outside consultants should become completely familiar with the criteria being used by the panelists for angiographic interpretation, and should engage in a pilot interpretation study, which is underway in the angiography panel.

8.8 CHEST ROENTGENOGRAMS

8.8.1 Introduction

Although there are significant questions concerning the value of the plain chest X ray in either suggesting or excluding the diagnosis of pulmonary embolism (1), the chest X ray will be interpreted in a formalized fashion during this study. In the individual institutions, the chest X ray will be used by the clinical scientist, by the angiographer, and in interpreting $\dot{V}/\dot{Q}$ isotope scans. The chest X ray will be interpreted locally by the clinical scientist and chest radiologist. The radiologist, in his usual fashion, will send a timely report to the clinical scientist and to the referring physician.

8.8.2 Official Interpretation for Study Purposes

The chest X ray will be forwarded to the Data and Coordinating Center. Every attempt will be made to obtain an erect PA and lateral film, but undoubtedly some of the studies will be done in the AP position as portable studies.

The Data and Coordinating Center will provide the X ray to the isotope scan interpretation panel and to the angiographic interpreters. Following its use for those functions, the chest X ray will be available for independent interpretation. Two individuals (one from Yale and one from Duke) on the angiographic panel are primarily chest radiologists. They will independently interpret all of the chest X rays with the exception of those that come from their individual institutions. A consultant who is expert on reading chest roentgenograms will be the second reader of the X rays from Yale and Duke. Thus, a consultant will read approximately one-third of the total X rays. A form will be completed at the time of the interpretation and will be forwarded to the Data and Coordinating Center. It is not felt necessary to have an adjudication concerning disagreement involving the findings on the plain chest roentgenograms.

8.8.3 Intra-Observer Variation

The Data and Coordinating Center will resubmit chest X rays in conjunction

with resubmission of angiographic studies, for re-interpretation by panel members in order to determine intra-observer variability of X ray readings.

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CHAPTER 9

FOLLOW-UP PROCEDURES

9.1 GOALS OF FOLLOW-UP EVALUATION

There are four major goals for follow-up: (1) to assess whether a normal $\dot{V}/\dot{Q}$ scan or an abnormal $\dot{V}/\dot{Q}$ scan in combination with a negative pulmonary angiogram rules out clinically important pulmonary embolism; (2) to determine prospectively the morbidity and mortality of pulmonary thromboembolism, that is, the clinical course of pulmonary embolism; (3) to compare patients randomly assigned to PIOPED angiographic pursuit to patients assigned to attending physician angiography decisions; and (4) to charterize the patient population not studied with PIOPED diagnostic imaging.

9.2 PATIENT GROUPS TO BE FOLLOWED

To realize the four goals of follow-up evaluation, PIOPED Clinical Centers will collect patient information after the acute phases of the illness(es) under investigation. The Clinical Centers will use three main methods to collect this data: first, post-discharge telephone interviews; second, post-discharge clinic visits; and third, post-discharge chart reviews. Post-discharge data collection schedules vary for different groups of patients in order to use PIOPED staff time efficiently and still provide the information needed to satisfy PIOPED goals. These patient groups are diagrammed in Exhibit 9-1.

PIOPED patient selection is based on random sampling from a population too large to investigate in the detail with which PIOPED investigators propose to collect information. Those patients randomly selected for No Contact will not be contacted for a telephone interview or clinic visit; nor will their charts be reviewed.

Those patients randomly selected to Recruit into PIOPED who decline the randomized study will be offered a chance to participate in PIOPED through a post-discharge chart review. Should any of these patients request that their charts not be reviewed, then not only will they not be contacted for a telephone interview or clinic visit, but their charts will not be reviewed for PIOPED data collection. The patients who decline the randomized study but do not decline chart review will be considered for post-discharge chart reviews. Since many more patients are expected to be eligible for post-discharge chart review than the PIOPED Clinical Centers have the resources to review, under Data and Coordinating Center direction, the Clinical Centers will review charts for a random sample of these patients. Patients characterized with a post-discharge chart review will not be contacted for telephone interviews or clinic visits. Those patients considered but not selected for post-discharge chart review will not be contacted for telephone interviews or clinic visits, and their charts will not be reviewed for PIOPED data collections.

Those patients who are selected randomly to Recruit into PIOPED, who grant informed consent, and who are randomized to attending physician angiography decisions will be contacted for telephone interviews at 1, 3, 6, 9 and 12 months after entry into PIOPED.

Those patients who are selected randomly to Recruit into PIOPED, who gran informed consent and who are randomized to PIOPED angiographic pursuit will be contacted for telephone interviews at 1, 3, 6 9, and 12 months after entry into PIOPED. Among these patients those with normal $\dot{V}/\dot{Q}$ scans, those with abnormal $\dot{V}/\dot{Q}$ scans and pulmonary angiograms negative for pulmonary emboli, and those with abnormal $\dot{V}/\dot{Q}$ scans and no pulmonary angiograms will be seen in their Clinical Centers for a history and physical examination at 3 months after entry into PIOPED.

Regarding the first goal, it is not certain how accurate a totally normal $\dot{V}/\dot{Q}$ scan or an abnormal $\dot{V}/\dot{Q}$ scan in combination with a negative pulmonary angiogram is in ruling out pulmonary embolism. Accordingly, close follow-up will be completed for patients with such findings including both a telephone contact administered at 1, 3, 6 and 12 months and a physical examination at three months.

In reference to the second goal, the study of clinical course, there are inadequate data in the literature addressing prospectively the course of pulmonary embolism and how the initial evaluation (i.e., history, physical examination, $\dot{V}/\dot{Q}$ scans, and pulmonary angiography) influences diagnosis, therapy, and outcome. This study will permit a prospective evaluation of diagnostic techniques and outcome in a group of approximately 150 patients.

Among the comparisons to be made between the attending physician angiography decision patients and PIOPED angiographic pursuit patients are (a) patient characteristics at time of entry into the study (e.g., age, sex), (b) extent of evaluation (i.e., whether pulmonary angiogram was performed), (c) final diagnoses, a (d) outcome (e.g., vital status one year after entry, embolic recurrence within one year).

In order to characterize the patient population not studied with PIOPED diagnostic imaging, chart review with collect data on demographic factors (age, sex, etc.), medical risk factors for pulmonary emboli (immobilization, medications, co-morbid states, etc.), physical examination (vital signs, etc.), and laboratory data (blood gas analyses, etc.).

9.3 METHODS AND EXTENT OF FOLLOW-UP

Clinical coordinators will conduct telephone interviews. These standardized interviews will inquire for the patient's vital status, for details of any rehospitalizations, for details of anticoagulation therapy, for serious bleeding complications, and for persistent or recurrent vascular problems such as thrombophlebitis or pulmonary embolism. Positive responses to inquires after thrombophlebitis or pulmonary embolism will prompt requests for hospital records and physician office records. If the interview gives any indication of recurrent embolism or venous thrombosis, the patient will be referred promptly to either the attending physician or PIOPED clinical scientist.

Clinical science fellows or clinical scientists will conduct clinic visits. These visits will include standardized medical history interviews and physical examinations. The clinical scientist or fellow will consult with the patient's attending physician(s) to obtain laboratory tests (e.g. chest X ray, electrocardiogram, $\dot{V}/\dot{Q}$ scan, pulmonary angiogram) as clinically indicated to investigate any suggestion of recurrent pulmonary embolism or venous thrombosis.

The telephone interview and clinic visit follow-up schedules for the different groups are displayed in Exhibit 9-2. The primary analysis of $\dot{V}/\dot{Q}$ scan sensitivity and specificity will be based on the original pulmonary angiogram interpretation for each case. Analysis results based on taking follow-up into consideration will be compared to the primary analysis to determine whether follow-up data changes the impression from original PIOPED classifications.

Chart review will be organized on a PIOPED study form to collect a portion of the same information collected on patients consenting to be recruited into the PIOPED randomized study. These chart reviews will be performed after the patient is discharged from hospital to remove any chance of PIOPED directly interfering with in-hospital management.

The PIOPED investigators expect to recruit about 1,000 patients for PIOPED angiographic pursuit including 100 patients with normal $\dot{V}/\dot{Q}$ scans, 750 patients with abnormal $\dot{V}/\dot{Q}$ scans but angiograms negative for pulmonary emboli and 150 patients with abnormal $\dot{V}/\dot{Q}$ scans and angiograms positive for pulmonary emboli. About 1,000 patients will be recruited for attending physician angiography decisions, and no more than 1,000 patients will be characterized with a post-discharge chart review. Thus over 3 years (2 years of recruitment and one of follow-up) each PIOPED Clinical Center expects to follow between 300 and 350 patients by telephone, perform a clinic visit on between 100 and 150 patients, and complete chart review on between 150 and 200 patients.

9.4 ROLE OF OUTCOME COMMITTEE

The Outcome Committee will consist of nine members as follows: one clinical scientist from each Clinical Center, one angiographer, one nuclear medicine physician and one representative of the Data and Coordinating Center. Working on cases referred to it from the Clinical Centers, the purpose of this committee will be to make final determinations, for study purposes, for all deaths and morbid events with respect to the presence or absence of embolism. The Committee will document each case as a) definite pulmonary embolism, b) suspected pulmonary embolism, c) no pulmonary embolism or d) insufficient information to determine pulmonary embolism status. The main information and review of these cases is provided by the clinical science component leader at the Clinical Center where the patient entered the study. This information and the clinical scientist's assessment will be entered on a standard study form for direct data entry when an autopsy report or pulmonary angiography has been provided or for Outcome Committee review in the absence of autopsy or angiography. The Outcome Committee offers a uniform method of classifying all such events, including the difficult and ambiguous cases, to eliminate the effect of local biases.

EXHIBIT 9-1

CHART OF PATIENT DISPOSITION AND FOLLOW-UP

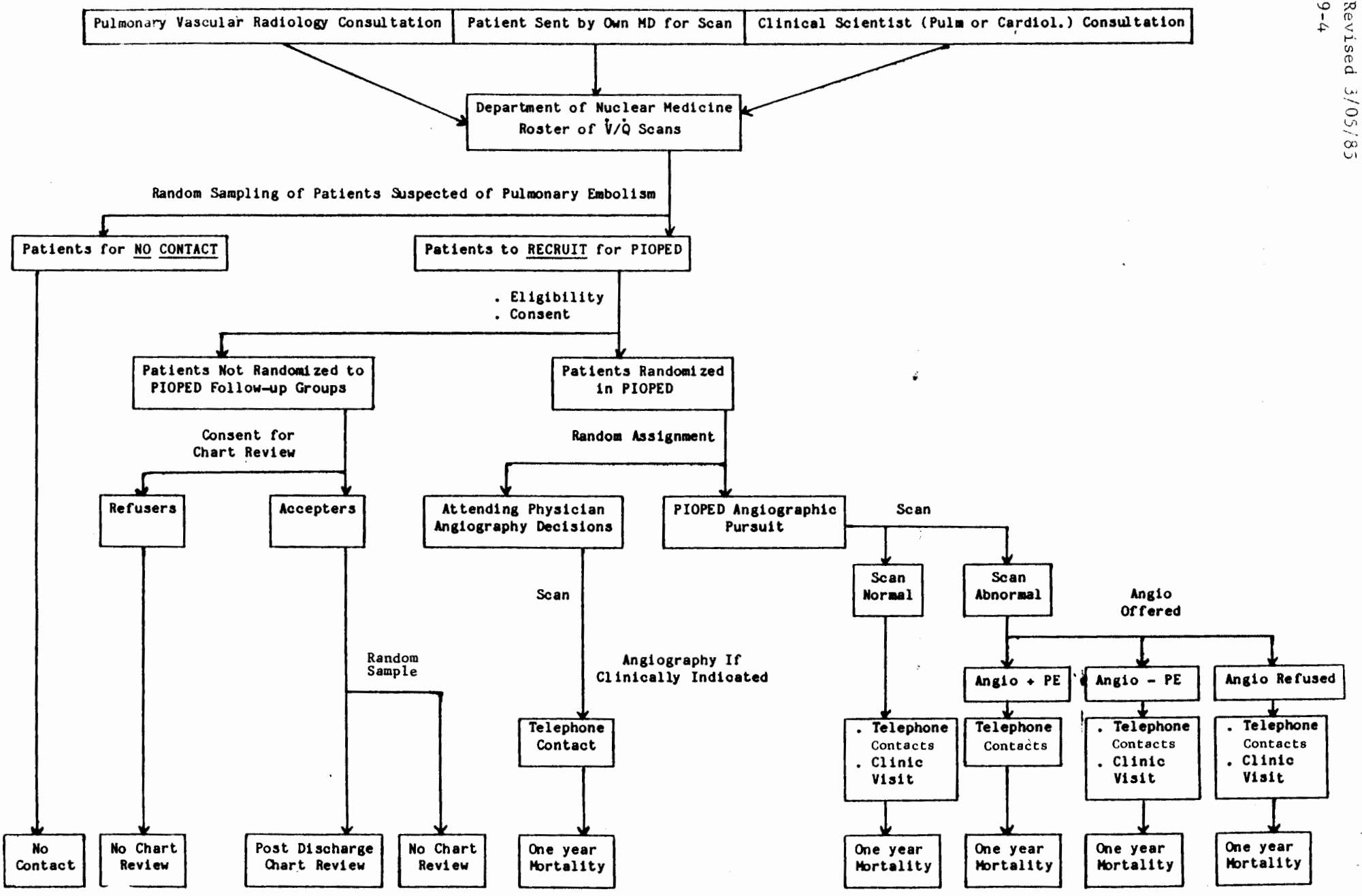


EXHIBIT 9-2

Follow-up Schedule

Follow-up Group	Month of Follow-up	Follow-up Procedures
PIOPED Angiographic Pursuit		
a) Scan Normal	1	Medical history by telephone
b) Scan Abnormal but	3	Physical and medical examinatio
Angiogram Negative	6	(after telephone contact)
for Pulmonary Emboli	9	Medical history by telephone
c) Scan Abnormal but	12	Medical history by telephone
Angiogram Not Done		
PIOPED Angiographic Pursuit		
a) Scan Abnormal and	1, 3	Medical history by telephone
Positive for Pulmonary	6,9	Medical history by telephone
Emboli	12	Medical history by telephone
Attending Physician		
Angiography Decisions	1, 3	Medical history by telephone
	6,9	Medical history by telephone
	12	Medical history by telephone

CHAPTER 10

ANALYSIS PLANS

10.1 PRIMARY ANALYSIS: SENSITIVITY AND SPECIFICITY

The primary analysis in this study will be of the sensitivity and specificity of $\dot{V}/\dot{Q}$ scans in diagnosing pulmonary embolism. Anatomic "Truth" as to whether pulmonary embolism is present or not cannot always be known. In these analyses, the angiographic determination of whether there is pulmonary embolism will be taken as giving the true state. The sensitivity and specificity of $\dot{V}/\dot{Q}$ scans will be estimated with respect to the subsequent diagnosis of pulmonary embolism from the angiogram. The patient will be the unit of measurement in this analysis and diagnosis of pulmonary embolism refers to diagnosis for a given patient.

10.1.1 Precision of Estimate in the 2 x 2 Case

Although in the following we will speak of $\dot{V}/\dot{Q}$ scans as if diagnostic of pulmonary embolism, this should be interpreted to mean V/Q scans that are abnormal and suggest pulmonary embolism. In the same way, non-diagnostic $\dot{V}/\dot{Q}$ scans, in this context, are $\dot{V}/\dot{Q}$ scans that are normal or not suggestive of pulmonary embolism. These definitions will vary for different analyses and will depend upon the cutpoint chosen in each situation. One of the aims of these analyses is to determine the cutpoint which will give us the largest values for sensitivity and specificity.

The analysis of sensitivity and specificity will be approached in several ways. The first approach will be using the 2 x 2 binary tables with patients classified as having $\dot{V}/\dot{Q}$ scans as if diagnostic or not of pulmonary embolism and with pulmonary angiograms diagnostic or not of pulmonary embolism.

In this 2 x 2 situation, the true underlying sensitivity of the lung scans can be considered a binomial random variable, say, p. The value of this unknown parameter is estimated from the data as $p = A/(A + C)$, using the usual notation for the two way table (Exhibit 10-1). That is, (A + C) is the number of patients with positive (diagnostic of pulmonary embolism) pulmonary angiograms, and A is the number with positive $\dot{V}/\dot{Q}$ scans and positive pulmonary angiograms.

Exhibit 10-1
$\dot{V}/\dot{Q}$ Scan and Angiogram Results Cross Classified

		Angiogram +	Angiogram −	Total
$\dot{V}/\dot{Q}$ Scan	+	A	B	A + B
	−	C	D	C + D
	Total	A + C	B + D	A + B + C + D

The standard error of this estimate $\hat{p}$ is estimated as s.e. = $(\hat{p}\ (1 - \hat{p})/n)$ where n is the denominator of p, that is, (A + C). Thus, the estimate of p and the standard error of the estimate are both functions of A and (A + C), both of which will come from the data of the study and are unknown quantities at this time. Therefore, any estimates of sensitivity and specificity made prior to the study will depend on prior estimates of the percentage of patients in the study who will show positive angiograms and of the percentage of those who will have positive lung scans. For example, suppose that of the expected total of 900 patients in the study who will have both $\dot{V}/\dot{Q}$ scan and angiogram, that 150 will have positive angiograms. (This is the hypothesized A + C). Suppose, further, that of these 150 patients, 121 will have positive V/Q scans (A = 121). Then the estimate of sensitivity is given by $\hat{p}$ = A/(A + C) = 121/150 = 0.81 and the estimated standard error is given by

$$\text{s.e.} = (\hat{p}\ (1-\hat{p})/n)^{1/2}$$

$$= [(0.81)(0.19)/150]^{1/2}$$

$$= 0.032$$

Ninety five percent confidence limits for the estimate of sensitivity are given by $\hat{p} \pm 1.96$ s.e., that in by $0.81 \pm (1.96)(0.032)$. This means we can be 95% certain that the true value of sensitivity lies in the range from 0.75 to 0.87.

Exhibit 10-2 gives the standard error for various possible outcomes of the number of patients with positive angiograms, (A + C), and of A/(A + C) (sensitivity) in the study, based on the overall expected number of 900 patients who will have $\dot{V}/\dot{Q}$ scans and pulmonary angiograms. In this table, the possible outcomes for sensitivity range from 0.50 to 0.95 in increments of 0.05, and the possible outcomes for the number of patients with positive angiograms range from 50 to 850 in increments of 50.

This table can be used to give the approximate standard error for almost any possible outcome of the study with respect to sensitivity. If desired, the standard errors can be used, as in the above example, to calculate 95% confidence intervals. In the example given above, sensitivity was 0.81 with 150 patients having positive angiograms and the standard error of the estimate was 0.032. The entry in this table for sensitivity of 0.80 and a denominator of 150 is 0.033; a very good approximation.

This table shows that, given the expected number of 900 angiograms to be done, for any reasonable set of assumptions about the outcome of the study, the precision of the estimates of sensitivity will be quite good. In fact, the biggest number in this table is the standard error of 0.071 which could occur if only 50 patients had positive angiograms and only 50% of those (i.e., 25) had abnormal $\dot{V}/\dot{Q}$ scans, which is a highly unlikely outcome.

Exhibit 10-2 can also be used to estimate the standard error of the estimates of specificity. Specificity can also be considered as a binomial random

variable estimated (from Exhibit 10-1) by $\hat{q} = D/(B + D)$, with standard error $[\hat{q}\ (1 - \hat{q})/(B + D)]^{1/2}$. In Exhibit 10-2 the column can be considered as outcome estimates of specificity and the rows as outcome possibilities for the number of patients with negative angiograms. The table entries then are the standard error of the estimates of specificity.

Exhibit 10-2

Standard Errors for Estimates of Sensitivity and Specificity*

No. of Pts. With Positive Angiograms	Estimated Sensitivity (Specificity)									
	.50	.55	.60	.65	.70	.75	.80	.85	.90	.95
50.	.071	.070	.069	.067	.065	.061	.057	.050	.042	.031
100.	.050	.050	.049	.048	.046	.043	.040	.036	.030	.022
150.	.041	.041	.040	.039	.037	.035	.033	.029	.024	.018
200.	.035	.035	.035	.034	.032	.031	.028	.025	.021	.015
250.	.032	.031	.031	.030	.029	.027	.025	.023	.019	.014
300.	.029	.029	.028	.028	.026	.025	.023	.021	.017	.013
350.	.027	.027	.026	.025	.024	.023	.021	.019	.016	.012
400.	.025	.025	.024	.024	.023	.022	.020	.018	.015	.011
450.	.024	.023	.023	.022	.022	.020	.019	.017	.014	.010
500.	.022	.022	.022	.021	.020	.019	.018	.016	.013	.010
550.	.021	.021	.021	.020	.020	.018	.017	.015	.013	.009
600.	.020	.020	.020	.019	.019	.018	.016	.015	.012	.009
650.	.020	.020	.019	.019	.018	.017	.016	.014	.021	.009
700.	.019	.019	.019	.018	.017	.016	.015	.013	.011	.008
750.	.018	.018	.018	.017	.017	.016	.015	.013	.011	.008
800.	.018	.018	.017	.017	.016	.015	.014	.013	.011	.008
850.	.017	.017	.017	.016	.016	.015	.014	.012	.010	.007

Note: The table is symmetric about 0.50. For estimates of sensitivity or specificity less than .50, enter the table using 1.0 minus the estimate. For example, if the estimate is 0.35, use the column for 0.65.

Section 10.2.7 gives an expanded example of the use of this table and the estimates of sensitivity and specificity based on the expected outcome of the study.

10.1.2 Imputation of Outcome for Normal $\dot{V}/\dot{Q}$ Scans

Some of the patients selected for pursuit to angiographic diagnosis will have absolutely normal $\dot{V}/\dot{Q}$ scans and hence will not be eligible for angiography. The question arises as to how to use the data for these patients in the assessment of sensitivity and specificity. Since there is no angiographic diagnosis, the decision remains to be made as to whether the outcome should be classified in cell C or D in Exhibit 10-1. (It is clear they must be in one of these cells since the V/Q scan is normal.)

For the purpose of analysis, it will be assumed that patients with normal $\dot{V}/\dot{Q}$ scans would be highly unlikely to have angiograms positive for pulmonary embolism if angiography were to be performed. This is quite a reasonable assumption (1) and is routine in medical practice (2). Imputation of angiography results receives more attention in the example in Section 10.2.7.

In 1982 the PIOPED Clinical Centers had the experience with $\dot{V}/\dot{Q}$ scans as indicated in Exhibit 10-3.

Exhibit 10-3

PIOPED Clinical Center $\dot{V}/\dot{Q}$ Scan Results (1982)

Clinical Centers	Number of $\dot{V}/\dot{Q}$ Scans in 1982	Percent of $\dot{V}/\dot{Q}$ Scans Read Locally as Normal
Duke	750	4.0
Henry Ford Hospital	302	36.8
Massachusetts General Hospital	524	19.0
University of Michigan	204	22.5
University of Pennsylvania	410	33.3
Yale	418	18.2

After discussing local differences in $\dot{V}/\dot{Q}$ scan interpretation criteria, the PIOPED investigators settled on scan interpretation criteria (see Chapter 7).

1. Normal

   - Pattern where the outlines of perfusion scan corresponds exactly to the shape of the lungs as seen on the chest X ray. Hilar and aortic impressions may be seen as minimal perfusion defects.

   - Chest X ray and/or ventilation study may be abnormal.

2. Very low probability

   - Three or fewer small (< 25% of a segment) perfusion defects with a normal chest radiograph, regardless of ventilation scan.

3. Low probability

   - Nonsegmental perfusion defects, e.g., very small effusion causing blunting of the costophrenic angle, cardiomegaly, enlarged aorta, hila and mediastinum, and elevated diaphragm.

   - Single moderate subsegmental (< 25% and > 75% of a segment) perfusion defect with normal chest X ray regardless of ventilation scan findings.

   - Any perfusion defect with a substantially larger chest X ray abnormality regardless of ventilation scan.

   - Large (> 75% of a segment) or moderate subsegmental (> 25% and < 75% of a segment) perfusion defects involving no more than four segments in one lung and no more than three segments in one lung region. These defects must have matching ventilation defects either equal to or larger in size and chest X ray either normal or with abnormalities substantially smaller than perfusion defects.

   - Multiple (more than three) small defects (< 25% of a segment) are low probability irrespective of number of defects, or ventilation scan findings.

4. Intermediate probability

   - All scans not falling in either normal, very low, low, or high probability categories will be designated as having intermediate probability for pulmonary embolism. When a study is considered "borderline high" or "borderline low," or the reviewer has difficulty categorizing it as low or high versus intermediate, the examination will be interpreted as intermediate.

5. High probability

   - Two or more large (> 75% of a segment) perfusion defects without ventilation or radiographic abnormalities.

   - Two or more large (> 75% of a segment) perfusion defects substantially larger than either matching ventilation or chest X ray abnormalities.

   - Two or more moderate subsegmental (> 25% and < 75% of a segment) and one large (> 75% or a segment) perfusion defect without matching ventilation or chest X ray abnormalities.

   - Four or more moderate subsegmental (> 25% and < 75% of a segment) perfusion defects without ventilation or chest X ray abnormalities.

These criteria would call normal a larger proportion of $\dot{V}/\dot{Q}$ scans than Duke called normal in 1982 (4.0%), and would assign the difference between that proportion (4.0%) and what the other Clinical Centers called normal (ranging from 18.2% to 36.8%) to a new category, "very low probability." No patients with normal $\dot{V}/\dot{Q}$ scans will be offered angiograms within the study. The PIOPED investigators expect the study's proportion of normal scans to lie between that for Duke's local readings in 1982 (4.0%) and Yale's readings in 1982 (18.2%). A reasonable and convenient number in that interval for study design purposes is 10.0%. Patients with very low probability V/Q scans will be offered angiograms. The normal and very low probability $\dot{V}/\dot{Q}$ scans pooled make up one natural cut-off for Receiver Operating Characteristic curve analysis of $\dot{V}/\dot{Q}$ scan data (see Section 10.1.3).

10.1.3 Receiver Operating Characteristic Curves

The classification of a $\dot{V}/\dot{Q}$ scan will not be a clear "Yes" or "No" with respect to diagnosis of pulmonary embolism. $\dot{V}/\dot{Q}$ scans will be categorized as normal (see Section 10.1.2), or with very low, low, intermediate, or high probability of pulmonary embolism. Some algorithms of classification may give rise to even finer gradings. However, in calculating sensitivity and specificity in the 2 x 2 case, each scan must be classified as negative or positive with respect to diagnosis of pulmonary embolism. This is done by choice of an arbitary cutpoint. For example, only normal and very low probability $\dot{V}/\dot{Q}$ scans might be considered as negative; or negative might also include low probability scans. With finer gradings of scans, almost an infinite number of possible cutpoints exist.

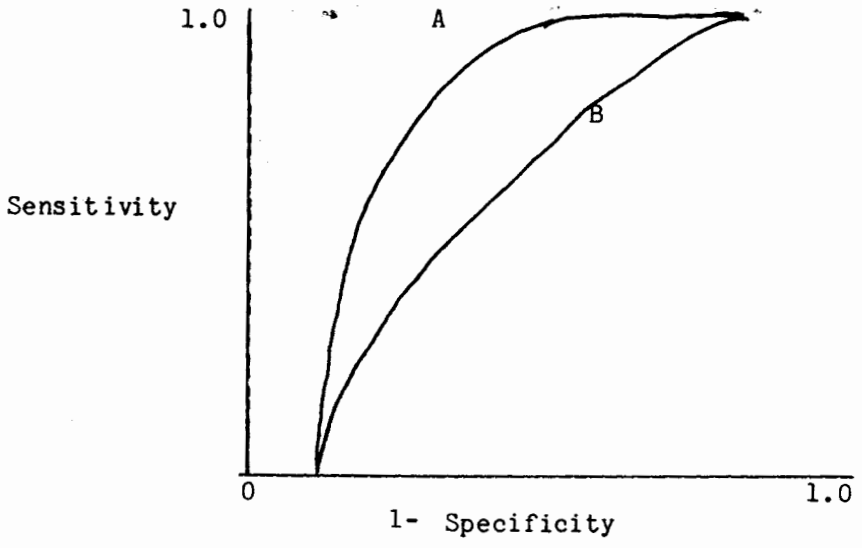
The choice of a cutpoint definitely affects the calculation of sensitivity and specificity. Calling more $\dot{V}/\dot{Q}$ scans positive increases the calculated value of sensitivity while it lowers the estimate of specificity. On the other hand, calling more $\dot{V}/\dot{Q}$ scans negative decreases the estimate of sensitivity and in-

creases that of specificity. An example of the trade off between sensitivity and specificity and the effect of choice of cutpoint is given in Section 10.2.6.

The question is how to choose an appropriate cutpoint for classification of $\dot{V}/\dot{Q}$ scans. One approach is to calculate sensitivity and specificity for a number of different cutpoints and to create a Receiver Operating Characteristic (ROC) curve (3). An ROC curve is simply a graph of sensitivity versus specificity where each point in the graph represents sensitivity and specificity for a given cutpoint. Exhibit 10-4 shows two hypothetical examples of ROC curves.

Exhibit 10-4

Typical Receiver Operating Characteristic Curve



Typically, as sensitivity increases, specificity decreases and vice versa. When sensitivity equals one (e.g., if all $\dot{V}/\dot{Q}$ scans were labelled positive), specificity is zero and when specificity equals one (e.g., if all $\dot{V}/\dot{Q}$ scans were labelled negative), sensitivity equals zero. Visual inspection of the ROC curve leads to the selection of a point on the curve where both sensitivity and specificity are relatively high. This point defines the cutpoint to be used for categorizing the $\dot{V}/\dot{Q}$ scan as positive or negative. Sensitivity and specificity do not have to have the same weight in determining the test (or method) with the most desirable characteristics.

ROC curves can be used to compare different tests or, in PIOPED, different algorithms based on the $\dot{V}/\dot{Q}$ scans to diagnosis pulmonary embolism. Each test will have different characteristics, i.e., relationships between sensitivity and specificity which can be illustrated by an ROC. In Exhibit 10-4, the test corresponding to the upper curve (say Test A) is obviously better than the test corresponding to the lower curve (say Test B), because at any level of specificity, the Test A is more sensitive than Test B, or, equivalently, at any level of sensitivity, Test A is more specific than Test B.

10.2 OTHER ANALYSES OF SENSITIVITY AND SPECIFICITY

The primary analyses of sensitivity and specificity discussed in Section 10.1 are for the 2 x 2 case using data from all patients and using only $\dot{V}/\dot{Q}$ scan data and angiographic outcome. Additional secondary analyses of sensitivity and specificity will be performed as discussed below.

10.2.1 Use of Clinical Data

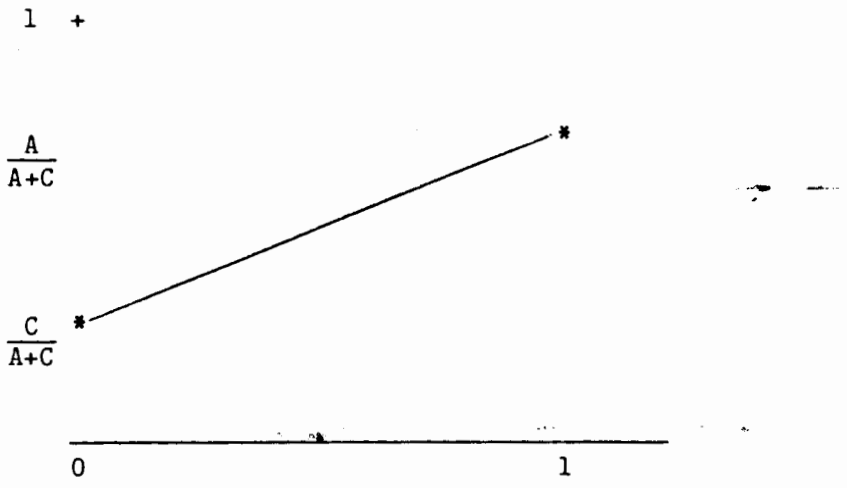
The cross-classification of $\dot{V}/\dot{Q}$ scan and angiographic outcome for the estimation of sensitivity and specificity as discussed in Section 10.1 did not make any use of the clinical data collected at the time of the patients' entry into the study. All of the analyses discussed in that section can be redone taking account of those data, including the chest X ray. The clinical data will be considered in classifying the $\dot{V}/\dot{Q}$ scan in terms of probability of positive angiogram. Then sensitivity and specificity can be calculated against the outcome of the angiogram. In addition, the clinical data alone can be considered in classifying the patients' probability of a positive angiogram and sensitivity and specificity can be calculated.

Comparison can be made of the estimates of sensitivity and specificity using the clinical data alone, the $\dot{V}/\dot{Q}$ scan data alone and the clinical data and $\dot{V}/\dot{Q}$ scan data together. (The use of ROC curves as discussed in Section 10.1.4 will be useful for this purpose.) These comparisons will demonstrate how much the inclusion of $\dot{V}/\dot{Q}$ scan data improves the accuracy of the diagnosis based on clinical data alone.

10.2.2 Categorical $\dot{V}/\dot{Q}$ Scan Data

The $\dot{V}/\dot{Q}$ scan data will not have a binary Yes - No outcome. At best, there will be a set of ordered categorical outcomes ranging from normal to high probability of pulmonary embolism. The first approach to analyzing these categorical data will be to combine the categories into two sets. For example, normal and very low probability $\dot{V}/\dot{Q}$ scans may be combined into a negative (no pulmonary embolism) category and all others into a positive category. A second analysis could include the low probability or even the intermediate probability scans in the negative category. Each different combination of categories will lead to different estimates of sensitivity and specificity. An ROC curve (Section 10.1.3) can be constructed from these and the optimum set of categories can be chosen.

Another approach to analysis of the case of categorical data is as follows. First, consider again the 2 X 2 situation, but only those cases with positive angiograms (i.e., the first column of Exhibit 10-1). There are A "positive" $\dot{V}/\dot{Q}$ scans out of A + C cases and C "negative" $\dot{V}/\dot{Q}$ scans. That is, the proportion of positive scans is A/(A+C) and of negative scans C/(A+C). These two percentages can be plotted and joined by a straight line as follows:



Here the points 0 and 1 on the abscissa are merely labels for the categories (negative and positive) and the ordinate values are the proportions. The equation for the straight line is

$$Y = a + bX,$$

where a = C/A+C and b = A/(A+C) - C/(A+C). Note that the sum of the values for the two parameters (a and b) is given by A/(A+C), which is the definition of sensitivity.

The paradigm can be extended to the case of (say) n categories. The proportion of positive $\dot{V}/\dot{Q}$ scans in each category can be plotted against the points 1, 2, ..., n, and a straight line fitted to those points using linear regression methods (4). The properties and usefulness of generalized definitions of sensitivity and specificity will be investigated during the course of the study.

10.2.3 "Continuous" $\dot{V}/\dot{Q}$ Scan Data

The $\dot{V}/\dot{Q}$ scan data do not necessarily have to be classified into a small fixed set of categories. The raw data from the V/Q scans can be used to derive a score for each $\dot{V}/\dot{Q}$ scan which can be interpreted as estimating the probability of a positive angiogram. The derivation of these scores can be based upon weights assigned to the various possible findings from the $\dot{V}/\dot{Q}$ scan and/or the clinical data. These weights will be determined by the investigators prior to the initiation of the study based upon their knowledge, experience and intuition. This is an extension of the approach by which $\dot{V}/\dot{Q}$ scans are classified as very low, low, intermediate, or high probability scans.

The derived "probability" scores will be used as the independent variables in the linear regression model,

$$y = \alpha + \beta X + \varepsilon .$$

Here, y represents the true, unknown, underlying probability of a positive angiogram given the estimated probability, X. Since the observed values of y can equal only zero (negative outcome) or one (positive outcome), the distribution of the errors is binomial with (unknown) parameter, y (4). The estimates of α and β can be derived by standard methods (4) and the estimate of β indicates how well the estimated "probability" scores correlate with the outcome. The "probability" scores can also be grouped into quantiles and the observed proportion of positive angiograms for each quantile will indicate how well the scores are related to outcome. Alternatively, the scores can be grouped into arbitrary categories and sensitivity and specificity calculated as discussed in Section 10.2.2.

Logistic models are often used in this kind of situation because the dependent variable is restricted to values between zero and one (5) and at the extremes of the range (of X values), the y-scores will approach zero and one. The logistic model will also be used in this regression approach. Results of the results using the linear and logistic models will be compared.

After study data have been collected, new algorithms to derive probability scores by using computer methods to search through the data to select the variables and associated weights which will give scores most related to the outcomes. These algorithms will be derived using a random half of the data set and tested on the remaining half. Results using these scores will be compared to those using the scores from the predetermined algorithm.

10.2.4 "Reassigned" Angiograms

Chapter 9 discusses cases in which diagnosis may be "reassigned" on the basis of clinical data or events occurring after the angiographic diagnosis of pulmonary embolsim has been made. Analysis will be performed of sensitivity and specificity of the $\dot{V}/\dot{Q}$ scans versus the angiograms including the reassignments. The primary analysis will be based on the original assignments of the angiograms. This secondary analysis using the reassignments will be to ascertain that such reassignments do not radically affect the estimates of sensitivity and specificity.

10.2.5 Subgroup Analysis

Sensitivity and specificity will will be calculated for subsets of patients. These analyses are secondary to the primary analysis of the total group and should be considered as being exploratory. Derived p-values must be interpreted conservatively because of the multiplicity of tests. Data and Coordinating Center Statisticians are considering Monte Carlo methods to simulate and anticipate the effects of this multiplicity.

The first subgrouping will be by Clinical Center to determine whether the results are consistent across centers. Other subgroupings will be based on:

1. Presence or absence of chronic obstructive pulmonary disease.

2. Patient's sex.

3. Patient's age.

4. History of previous pulmonary embolism.

5. Ambulatory (emergency room) patients versus intensive care patients.

6. Surgical versus medical patients.

7. Chronic cardiopulmonary disease patients versus other patients.

8. Pulmonary vasculitis known to be present versus not known to be present.

9. Patients with normal chest X rays vs. patients with abnormal chest X rays.

10. Other baseline characteristics.

Subgroup estimates will be useful for generalizing the results of this study to groups and institutions dissimilar to the PIOPED centers. For instance an institution may see only ambulatory medical patients with no history of pulmonary embolism. Another institution may be interested in the sensitivity and specificity of $\dot{V}/\dot{Q}$ scans in surgical patients, etc.

10.2.6 The Patient as the Unit of Analysis

Above, sensitivity and specificity of $\dot{V}/\dot{Q}$ scans were analyzed using the patient as the unit of analysis. For a secondary analysis, the data for each lung will be analyzed. That is, the question will not be whether the patient's $\dot{V}/\dot{Q}$ scan and angiogram are positive or negative but rather whether the $\dot{V}/\dot{Q}$ scan and angiogram findings are concordant for the presence or absence of defects localized to the lobar level in a given lung. For this analysis, the Clinical Centers will be grouped according to whether the center's procedure is to angiograph the second lung after pulmonary embolism has been confirmed in the first lung. Analysis will be done separately for these two groups of centers.

10.2.7 Expected Findings

The following discussion of the expected outcome of the study illustrates some of the analysis approaches under consideration.

Of the 1,000 patients randomly selected for pursuit to angiographic diagnosis it is expected (see Chapter 2) that the outcome of the $\dot{V}/\dot{Q}$ scans will be as follows:

High probability - 100 $\dot{V}/\dot{Q}$ scans

Intermediate probability - 200 $\dot{V}/\dot{Q}$ scans

Low probability - 400 $\dot{V}/\dot{Q}$ scans

Very low probability - 200 $\dot{V}/\dot{Q}$ scans

Normal - 100 $\dot{V}/\dot{Q}$ scans

It is further expected (see Chapter 2) that, overall, 150 patients will have positive angiograms. Exhibit 10-5 displays a possible breakdown of this outcome according to $\dot{V}/\dot{Q}$ scan findings.

Exhibit 10-5

Possible Study Outcome

	Positive	Negative	Total
High probability	85	15	100
Intermediate probability	36	164	200
Low probability	20	380	400
Very low probability	6	194	200
Normal	3*	97	100
Total	150	850	1,000

*Imputed value

Here, the imputed outcome for the normal $\dot{V}/\dot{Q}$ scans (see Section 10.1.2) is taken to be the proportion (3%) of positive angiograms expected in the very low probability group. In order to test the effect of this assumption on the estimate of sensitivity and specificity, other calculations will be made where all of the normal $\dot{V}/\dot{Q}$ scans will be assigned normal pulmonary angiograms. On the other hand, if the proportion of positive pulmonary angiograms among patients with very low probability $\dot{V}/\dot{Q}$ scan is higher than expected, a change in the study protocol might be considered whereby patients with normal $\dot{V}/\dot{Q}$ scans might go on to angiography; the reasoning being that if a large percentage of very low probability $\dot{V}/\dot{Q}$ scans are associated with positive angiograms, a fair proportion of normal scans might also be thus associated. Decision rules for this possible change in protocol are discussed in Section 10.4.1. The expected proportion of positive angiograms for the low, intermediate, and high probability groups are 5%, 18%, and 85%, respectively.

As discussed in Section 10.1.3, the five categories of $\dot{V}/\dot{Q}$ scan outcome can be defined in different ways for the creation of a binary table of classification. Each different choice of a cutpoint (i.e., definition) for $\dot{V}/\dot{Q}$ scans indicative of pulmonary embolism (i.e., "positive" scan) will lead to a different table and different estimates of sensitivity and specificity. For example, if only high probability scans are called positive, the outcome table can be seen in Exhibit 10-6.

Exhibit 10-6

One ROC Point in Possible Study Outcome Analysis

		Angiogram		
		Positive	Negative	Total
$\dot{V}/\dot{Q}$ Scan	"Positive"	85	15	100
	"Negative"	65	835	900
	Total	150	850	1,000

The estimate of sensitivity is 57% (85/150) and of specificity, 98% (835/850). From Exhibit 10-2, the standard errors for these estimates are .041 and .007, respectively. Exhibit 10-7 displays the estimates of sensitivity and specificity and their approximate standard errors for the different combinations of $\dot{V}/\dot{Q}$ scan categories using the data given in Exhibit 10-5.

Exhibit 10-7

Sensitivity and Specificity for Different Combinations of $\dot{V}/\dot{Q}$ Scan Data

Categories Included as "Positive" $\dot{V}/\dot{Q}$ Scans	Estimated Sensitivity	Estimated Specificity	Standard Errors Sensitivity	Specificity
High Probability Scans Only	0.57	0.98	.041	.007
Intermediate and High Probability Scans	0.81	0.79	.033	.014
Low, Intermediate and High Probability Scans	0.94	0.34	.018	.012
Very Low, Low, Intermediate and High Probability Scans	0.98	0.11	.018	.010

These data can be used to construct an ROC curve (see Section 10.1.3). In this example, the choice of a definition (cutpoint) which leads to reasonably large estimates of both sensitivity and specificity is to label all intermediate and high probability V̇/Q̇ scans as "positive" or indicative of pulmonary embolism and all others as "negative." With this dichotomy, sensitivity is estimated as .81, specificity as .79. With the given study size, the standard errors for these estimates are .033 and .014, respectively so that the 95% confidence limits for the estimates are fairly narrow.

10.3 OTHER ANALYSES

10.3.1 Prediction Algorithms

The PIOPED data set can also be used to develop models to predict presence of pulmonary embolism from patient characteristics. Percentiles of risk for pulmonary embolism express these findings in a clinically useful way. In this analysis, it is more reasonable to use logistic models (5) which restrict the estimates of probability to values between zero and one.

Comparison can be made of the predictive values from different models where the independent variables are derived from the baseline clinical data, and/or V̇/Q̇ scan data to determine which of these components is most related to the angiographic diagnosis of pulmonary embolism.

10.3.2 Comparability of Study Groups

As discussed in Section 9.1, the study population is randomized into two major groups, patients for PIOPED angiographic pursuit and patients to follow their attending physician's angiography decisions. Patients who decline entry into the study are also of interest as they represent the effects of selection which may limit generalization from study results. In particular, it will be important to recognize differences among all the groups at baseline. To this end, analyses will be performed to describe and compare the baseline characteristics of the various groups. Data to be analyzed will include demographic data, medical history (especially chest and cardiac) data, physical examination data, chest X ray data, and laboratory studies.

The various groups will also be compared for outcome data. It will be important to find out whether or not those patients randomized to PIOPED angiographic pursuit, and those randomized to attending physician angiography decisions have the same outcome pattern. It will also be important to note what the differences in outcome are among patients with normal V̇/Q̇ scans, those with negative angiograms and those with positive angiograms. The outcome data to be analyzed will include mortality, cause-specific mortality, hospital admission for suspected and/or documented pulmonary embolism (not including the event which made the patient eligible for the study), and other medical events during the follow-up period.

10.3.3 Analysis of Reliability of $\dot{V}/\dot{Q}$ Scan and Angiogram Readings

The procedures for reading $\dot{V}/\dot{Q}$ scans and pulmonary angiograms are discussed in Chapters 7 and 8, respectively. Each $\dot{V}/\dot{Q}$ scan and angiogram will be read at least twice by study investigators and outside reviewers. Analysis of percent agreement will be made, and Kappa statistics (6) will be calculated to compare readings between the investigators and betweeen the study investigators and the outside reviewers. Agreement will be checked on several levels. For example, for the pulmonary angiograms, comparisons will be made of positive and negative readings as well as for agreement on specific findings such as lobes or segments involved. See Chapter 12 for additional discussion of this topic.

10.4 MONITORING STUDY PERFORMANCE

In addition to the analyses of study results as discussed above, other analyses will be performed during the course of the study to monitor the progress and performance of the study.

10.4.1 Angiographic Outcome for Very Low Probability $\dot{V}/\dot{Q}$ Scans

As discussed in Chapter 2, patients with $\dot{V}/\dot{Q}$ scans with very low probability of pulmonary embolism will be angiogrammed. Particular attention will be paid during the course of this study to the angiographic outcome for these patients. Data reports showing the proportion of positive angiograms for these patients will be presented to the Policy and Data Safety Monitoring Board.

The purpose in monitoring these data is to ascertain that the proportion of positive angiograms is neither too high or too low. If the proportion is too low, it may be ethically necessary to discontinue angiograms on patients with very low probability V/Q scans. On the other hand, if the proportion of positive angiograms were too high, it might be decided that patients with normal $\dot{V}/\dot{Q}$ scans also ought to be angiogrammed.

The Policy and Data Monitoring Board will be responsible for advising NHLBI and Steering Committee when low and high thresholds are reached. The Data and Coordinating Center will report the percentage as well as estimates of precision for the observed percentage to the Policy and Data Safety Monitoring Board. For example, suppose that the Board decides that there should be at least a 5% chance of patients with very low probability $\dot{V}/\dot{Q}$ scans to have positive angiograms in order that such patients continue to be angiogrammed. It is expected that after one year of patient enrollment, there will be 100 patients with very low probability $\dot{V}/\dot{Q}$ scans. Suppose that of these 100 patients, two subsequently have angiograms positive for pulmonary embolism. The exact probability of observing two or fewer positive angiograms when the probability of a positive angiogram for any single such patient is 5%, is calculated using binomial probability (4) to be 0.12. Hence, observing two positive angiograms in this subgroup of 100 patients is statistically consistent with a true underlying probability of 5% and angiography could continue in very low probability $\dot{V}/\dot{Q}$ scan patients. On the other hand, if there were only one positive angiogram in this subgroup of 100 patients, the probability of such a small number of occurrences is 0.037.

Hence, it could be concluded with 95% confidence that the probability of a positive angiogram in very low probability $\dot{V}/\dot{Q}$ scan patients is less than 0.05 and the Board could recommend discontinuing angiogramming such patients.

The Board may also decide that if there is a 20% chance or more that very low probability $\dot{V}/\dot{Q}$ scan patients have positive angiograms, that patients with normal $\dot{V}/\dot{Q}$ scans also should be angiogrammed. Again with 100 very low probability $\dot{V}/\dot{Q}$ scan patients, if 27 had positive angiograms, the probability of such an occurrence is only .034 when the probability of a single such event is 0.20. Hence, observing 27 or more such events in 100 cases could cause the Board to decide that patients with normal $\dot{V}/\dot{Q}$ scans should receive angiography.

10.4.2 Inferior Venacavography

The proportion of patients who have positive inferior venacavograms will also be monitored closely using the procedures discussed in Section 10.4.1. If the proportion of patients with positive inferior venacavograms is too low, the Policy and Data Monitoring Board may recommend to drop this procedure from the study protocol. For example, the Board may decide that if the chance of a positive inferior venacavogram is less than 5% in patients with positive angiograms, that the procedure be discontinued. After a year of patient enrollment, it is expected that there will be 75 patients with positive angiograms. The probability of exactly one patient out of 75 having a positive inferior venacavogram is .084 when the probability for any single event is .05. Hence, the Board could conclude with 95% confidence that this probability is less than .05 only if there were zero positive inferior venacavograms among the first 75 patients with positive angiograms.

10.4.3 Enrollment

The Data and Coordinating Center will be responsible for monitoring the enrollment of patients at each Clinical Center and for adjusting the randomization schedule as necessary to assure a uniform and equal flow of patients into the study at each center.

10.4.4 Data Monitoring Reports

Results of the analyses discussed above will be gathered into a Data Monitoring Report which will be prepared four times a year for distribution to the Policy and Data Safety Monitoring Board. The Board will meet twice a year to review these reports. Portions of the reports will be distributed to the Steering Committee after review and approval for such distribution by the Board.

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CHAPTER 11

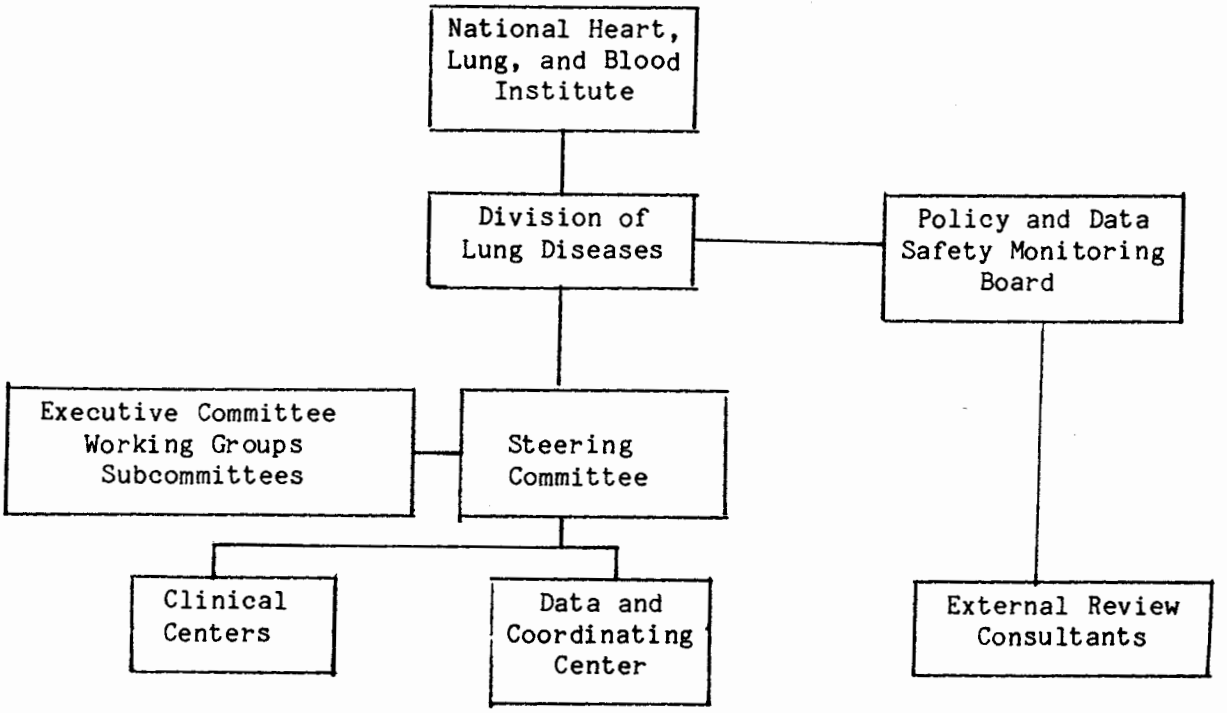
ORGANIZATIONAL STRUCTURE

11.1 INTRODUCTION

The organizational components of this study include participating units and administrative units. The participating units are: individual Clinical Centers, a Data and Coordinating Center, External Review Consultants, and the National Heart, Lung, and Blood Institute. The administrative units are: a Policy and Data Safety Monitoring Board, a Steering Committee, an Executive Committee and several working subcommittees established by the Steering Committee.

Exhibit 11-1

Organizational Chart



11.2 PARTICIPATING UNITS

The duties and responsibilities of the participating units in this study are described below.

11.2.1 Clinical Centers

Each Clinical Center is responsible for recruiting the required number of patients, administering the clinical evaluation and diagnostic tests as required

by the study protocol, obtaining follow-up information, and collecting, recordi and forwarding patient data to the Data and Coordinating Center. The professio and clerical organization of each Clinical Center will include a clinical scientist, a nuclear medicine specialist, an angiographer, and a clinical coordinator. The Principal Investigator will be a member of the Steering Committee and will be responsible for the ongoing operation of the study. The clinical coordinator will be responsible for obtaining follow-up data, checking the completeness of data and forwarding it to the Data and Coordinating Center, and shipping scans and angiograms to the Data and Coordinating Center. Clinical Center staff have agreed to meet twice a month to review local study progress, report on work completed and bring up operational problems some of which may be brought to studywide attention by the Clinical Center's Principal Investigator. The Principal Investigators have a forum for considering studywide problems in the Steering Committee (see Section 11.3.2) and more immediately in PIOPED Principal Investigators' conference telephone calls. These conference telephone calls are planned for every second month except those months when there is a Steering Committee meeting.

The Institutions participating in the study as Clinical Centers and their respective Principal Investigators are listed below.

1. Duke University
   Durham, North Carolina
   Dr. Herbert A. Saltzman, Principal Investigator

2. Henry Ford Hospital
   Detroit Michigan
   Dr. Paul D. Stein, Principal Investigator

3. Massachusetts General Hospital
   Boston, Massachusetts
   Dr. Charles A. Hales, Principal Investigator

4. University of Michigan
   Ann Arbor, Michigan
   Dr. John G. Weg, Principal Investigator

5. University of Pennsylvania
   Philadelphia, Pennsylvania
   Dr. Abass Alavi, Principal Investigator

6. Yale University
   New Haven, Connecticut
   Dr. Richard H. Greenspan, Principal Investigator

11.2.2 Data and Coordinating Center

The Data and Coordinating Center plays a major role in the design, implementation, and execution of the study. The Data and Coordinating Center will be represented on, and work under the direction of the Steering Committee. The

staff of the Data and Coordinating Center has the responsibility of collecting, editing, storing, and analyzing all data received from the Clinical Centers and the External Review Consultants. Among the specific functions of the Data and Coordinating Center are:

1. To participate with the investigators in the development of the study protocol, data reporting procedures, and the Manual of Operations.

2. To pretest the procedures for data recording, processing, and reporting.

3. To make random assignment of patient entry into the study.

4. To review and edit all data transmitted to the Data and Coordinating Center.

5. To participate in the establishment and monitoring of quality control procedures.

6. To provide statistical analyses of all study data.

7. To receive and distribute scans and angiograms for independent review.

8. To check the completeness of records and periodically prepare performance reports to participating Clinical Centers.

9. To analyze periodically the frequency of adverse side effects of the diagnostic procedures and to report this data to the Policy and Data Safety Monitoring Board.

10. To prepare interim technical and statistical reports for the study participants and the Steering Committee.

11. To monitor patient recruitment at each Clinical Center.

12. To assist in the preparation of reports of the study for publication.

The Data and Coordinating Center staff meet weekly to review study progress, report on assigned work and receive work assignments to fulfill the Data and Coordinating Center specific functions.

The Maryland Medical Research Institute, 600 Wyndhurst Avenue, Baltimore, Maryland 21210 is the Data and Coordinating Center for this study. Dr. Michael Terrin is the Data and Coordinating Center Principal Investigator for this project.

11.2.3 External Review Consultants

The panel will consist of two radiologists and two nuclear medicine specialists from outside the participating institutions who will be appointed by the DLD. Two internists may be added to the panel at the discretion of DLD. The specific duties of the panel will include an annual visit to each participating Clinical Center to assure the use of uniform criteria in the reading and interpretation of scans and angiograms and to monitor inter- and intra-observer variability in the reading of scans and angiograms. Their data will be reported to the Data and Coordinating Center. Their recommendations will be reported to the Policy and Data Safety Monitoring Board.

11.2.4 National Heart, Lung, and Blood Institute Project Office

The Division of Lung Diseases (DLD), National Heart, Lung, and Blood Institute, as sponsor of the study, is responsible for providing organizational, scientific, and statistical direction to the study through the Interstitial Lung Diseases Branch. The Scientific Project Officer is a voting member of the Steering Committee and a non-voting member of the Policy and Data Safety Monitoring Board. The Contract Officer is responsible for all administrative and fiscal matters related to the award and conduct of the contracts.

11.3 ADMINISTRATIVE UNITS

The participating units of the study are coordinated by the DLD, the Policy and Data Safety Monitoring Board, and the Steering Committee.

11.3.1 Policy and Data Safety Monitoring Board

The Policy and Data Safety Monitoring Board acts in a senior advisory capacity to the DLD on policy matters throughout the duration of the study. In addition, it periodically reviews study results and evaluates the study diagnostic procedures for beneficial and adverse effects.

The Board is composed of a chairman and additional voting members, who are appointed by the DLD for the duration of the study. The Scientific Project Officer, as an ex-officio member, is a non-voting member of the Board. Board meetings are attended, when appropriate, by senior representatives from the Data and Coordinating Center and the chairman of the Steering Committee. Additional Board members or consultants may be appointed, if deemed necessary, by the DLD in response to recommendations by the Board. No voting member of the Policy and Data Safety Monitoring Board may participate in the study as an investigator; however, other investigators from the Board member's institution will not be excluded from participating in the study. The Board will meet no less than twice a year.

Specific functions of the Policy and Data Safety Monitoring Board are:

1. To review and approve the study protocol and Manual of Operations.

2. To review and analyze the progress of the study, including the clinical data to evaluate its relevance to the program goals.

3. To monitor the study diagnostic procedures for beneficial and adverse effects on the patient.

4. To approve major changes in the protocol or Manual of Operations and make recommendations to the DLD.

5. To review and approve ancillary studies (with the possible effect on the main study being the major criterion).

6. To assist the DLD in resolution of problems referred by the Steering Committee.

7. To make recommendations to the DLD on any proposed early termination of the study because of adverse effects of any diagnostic procedure.

8. To recommend remedial measures or discontinuation of individual Clinical Centers which perform unsatisfactorily.

11.3.2 Steering Committee

The Steering Committee provides scientific direction to the study at the operational level. The voting members of the Steering Committee are one member from each Clinical Center and the Data and Coordinating Center, and the DLD Project Officer. Specific functions of the Steering Committee are:

1. To make recommendations to the Policy and Data Safety Monitoring Board concerning changes in the protocol and Manual of Operations.

2. To review and analyze the progress of the program.

3. To review all proposed ancillary studies and to report all recommendations to the Policy and Data Safety Monitoring Board (the major criterion being the possible effect on accomplishing the objectives of the main study).

4. To monitor the performance of the individual Clinical Centers with regard to patient recruitment and patient follow-up studies.

5. To be responsible for the presentation of the program results to the biomedical community.

The Steering Committee will meet no less than twice a year. Additional meetings of the Steering Committee will be held as necessary.

11.3.3 Working Groups

Three Working Groups constitute standing committees of the study -- the Angiography Working Group, the Clinical Science Working Group and the Nuclear Medicine Working Group. Voting members of each working group include one representative from each Clinical Center, one representative from the Coordinating Center, and one representative from the Project Office. For each Clinical Center, the Angiography Working Group regular member is the angiographer in charge of each angiography component; the Clinical Science Working Group regular member is the cardiologist, internist or pulmonary disease specialist in charge of each clinical science component; and, the Nuclear Medicine Working Group regular member is the nuclear medicine specialist in charge of each nuclear medicine component. Specific functions of the Working Groups are:

1. To develop operational procedures for specialists in their respective Working Group.

2. To review and discuss difficult studies.

3. To report to the Steering Committee on study procedures and data collection in their respective areas of speciality.

4. To report to the Executive Committee with detailed review of source documents on multi-disciplinary issues.

5. To keep all component leaders for the Clinical Centers, the Coordinating Center representatives, and the Project Office informed of progress in implementing uniform procedures in the Clinical Centers.

6. To provide a forum for component leaders to discuss state of the art issues in their respective areas of speciality and as they relate to PIOPED.

11.3.4 Executive Committee

The Executive Committee will meet between Steering Committee meetings to review interdisciplinary issues on the Steering Committee agenda. Voting members of the Executive Committee are the Chairman, the Co-Deputy Chairmen, the Director of the Data and Coordinating Center and the DLD Project Officer. Specific functions of the Executive Committee are:

1. To make recommendations to the Steering Committee concerning interdisciplinary issues.

2. To assign to Working Groups responsibility for detailed review of source information on issues with interdisciplinary implications.

3. To review clinical science, nuclear medicine and angiography procedures for consistency with each other.

4. To review data collection and interpretation issues for compatibility across the study disciplines.

5. To promote communication within centers through feedback on interdisciplinary issues to the Working Groups.

CHAPTER 12

CONDUCT OF THE STUDY

12.1 INTRODUCTION

To achieve the objectives of this large-scale multicenter trial, it is necessary to successfully integrate the efforts of many study personnel, deal effectively with many patients, and efficiently handle a large volume of study data. Before patient recruitment begins, the investigators will train each other in standardized aspects of the protocol. The Data and Coordinating Center (DCC) will closely monitor study data and the flow of information between study centers. The Steering Committee and sub-committees will review periodic data reports. Quality control procedures will be implemented. Study training, monitoring, data review and quality control are all specifics essential to PIOPED's success as a multicenter study. They are not limited to any area of professional expertise. However, their explicit description is essential for the many centers and disciplines in PIOPED to be sure they are performing their tasks synchronously with each other.

12.2 TRAINING

Three Working Groups - the Clinical Sciences Working Group, the Nuclear Medicine Working Group, and the Angiography Working Group - were formed during the organizational phase of this study. Each Working Group was charged with developing and implementing appropriate procedures for their respective roles in patient recruitment, evaluation and follow-up. These charges included specification of procedures to be conducted, technical quality control of those procedures, and interpretation of procedures. Each study Clinical Center was represented on each Working Group by the investigator from that center who will have primary repsonsibility for the conduct of those aspects of the trial relating to his Working Group. Thus, training for implementation of the protocol has been built into the study design, as those responsible for implementation have designed their respective parts of the protocol. Working Group members will be required to train physicians and staff locally at their Clinical Centers. A central training session is also planned prior to Phase II, and will involve training in standardization of procedures. Continuing uniform implementation of the protocol will be achieved by continued meetings of the groups during the course of the trial. New investigators will join these meetings and thus be immersed in the workings of these groups.

Quality control procedures will insure study-wide uniform procedures, interpretation and reporting of results, and monitor for drift over time. Consultants from outside the study will be employed as part of this quality assurance. Quality control procedures, are summarized in Section 12.4

Upon completion of form development, study personnel will be trained by Data and Coordinating Center staff in uniform completion and processing of study materials.

12.3 DATA EDITING AND MANAGEMENT

12.3.1 Data Processing

The completed and keyed study forms will be edited by computer for several types of deficiencies and errors.

1. Unanswered or illegible items.
2. Values of quantitative variables which are outside preset ranges.
3. Values of qualitative response which are not permissible (often due to keypunch errors).
4. Inconsistencies among items within a form.
5. Inconsistencies among forms from different visits for specific variables.
6. Patient identification, follow-up visit number, and follow-up visit date errors or inconsistencies.

For each detected error a correction procedure will be initiated. For errors not originating in the Data and Coordinating Center, the Clinical Center staff will be required to complete correction forms and send them promptly to the Data and Coordinating Center in order to correct the computer data file.

A computer inventory of all forms received at the Data and Coordinating Center for each patient will be developed and maintained. This inventory will make it possible to generate a list of study forms which are past due and to send such lists to the investigators. Another computer file will contain the keyed data from all of the study forms received from the Clinical Centers. This file will be structured to allow easy addition of new follow-up forms for each patient and will be designed so that all of the forms for a given patient can be linked together to facilitate analysis.

12.3.2 Data Form Handling

$\dot{V}/\dot{Q}$ scan films and angiography films will be sent to the Data and Coordinating Center with their associated local interpretations. Data and Coordinating Center staff will then mail appropriate materials to other study investigators and consultants for interpretation. The materials will be sent to investigators from centers other than the one where the films were taken. After interpretations are made, study films and forms will be returned to the Data and Coordinating Center. For both angiograms and $\dot{V}/\dot{Q}$ scans, Data and Coordinating Center staff will send the films for a third grading if there are interpretation discrepancies. Two certified nuclear medicine investigators will travel to the Data and Coordinating Center for a consensus grading of $\dot{V}/\dot{Q}$ scans.

12.3.3 Follow-up Data

At the time the Data and Coordinating Center receives a form indicating that a patient has been enrolled in the trial, it will generate an appointment schedule listing the expected dates and permissible time windows around these dates for completion of the follow-up inquiries (telephone contacts or clinic visits). For telephone contacts, time windows are designed so one is always open. If a patient is beyond time limits for a telephone contact, that data will not be rejected, but will be accepted into the next time period to avoid unnecessary loss of data. For the one month telephone contact, the time window will extend from hospital discharge or one month after study entry (whichever should come first) up to the start of the second month post-study entry. For the three month telephone contact, the time window will extend from two months' post-study entry up to the start of the fourth month post-study entry. For the six month telephone contact, the time window will extend from four months post-study entry up to through twelve months post-study entry. One year mortality will be completed after the twelfth month post-study entry. For the sake of efficiency and as a point in monitoring study quality control, telephone contacts are to be completed as close to the assigned date as possible.

The clinic visit at three months post-study entry is scheduled only for patients in the PIOPED angiographic pursuit group with normal scans, normal angiograms or no angiograms. For this visit the time window will extend from two months post-study entry up to the start of the fourth month post-study entry. Schedules will be sent to the clinics to aid in timing patient contacts.

All fatal events as well as hospitalizations for specified events will be reported on a study form completed by the clinic investigators and submitted to the Data and Coordinating Center. At the request of the clinic investigator, the Data and Coordinating Center may attempt to locate patients who have been lost to follow-up to determine their vital status. Study forms on which the fatal events and hospitalizations are recorded will become a part of the computer files. Events reported by Clinical Center Principal Investigators as documented by autopsy or angiography will be automatically classified. Those events not automatically classified according to study criteria will be reviewed by the Outcome Committee.

A physician responsible for processing the event reports at the Data and Coordinating Center will receive copies of all forms on which these events are reported as well as any accompanying documentation of the events such as ECGs, X rays, hospital summaries, autopsy reports, death certificates, etc. When all the required information has been collected for a particular event, the records will be sent to the Outcome Committee which will either classify the event or ask for more information. The evaluation of the committee will be added to the computer files.

12.3.4 Data Forms Audit

Periodically, selected items of data in the computer file will be listed

in a compact but readable form -- one or two pages per patient -- and sent to the investigator. He/she will then be able to check whether the data recorded in the Data and Coordinating Center electronic file correspond to the data in the clinic records. Some investigators find these lists helpful for patient management purposes.

12.4 QUALITY CONTROL PROCEDURES

12.4.1 Monitoring the Clinical Centers

One aspect of quality control will consist of performance reports generated by computer. Such reports will include:

1. Patient enrollment, by Clinical Center.
2. Number and percentage of forms with detected errors, by Clinical Center.
3. Number of delinquent forms, by Clinical Center.
4. Number of delinquent radiographic studies, by Clinical Center.
5. Quality of $\dot{V}/\dot{Q}$ scan and angiographic studies, by Clinical Center.
6. Comparison of local interpretations of scans and angiographics with official study interpretations, by Clinical Center.

Other indicators of work progress and adherence to protocol will be summarized periodically. Reports will be prepared giving, by Clinical Center, comparisons of scan results with angiographic interpretation for pulmonary embolism.

Each Clinical Center will receive on a regular basis a telephone call in order to review procedures, discuss problems, and receive suggestions concerning possible improvements in that center's procedures. Site visits to resolve problems may be scheduled at the discretion of the Steering Committee, DLD Project Office, and/or Policy and Data Safety Monitoring Board.

12.4.2 Quality Control of the Data and Coordinating Center

In developing the procedures for inventory and data entry of study forms, the individual designated as Quality Control Supervisor for the study at the Data and Coordinating Center and appropriate programming staff will develop procedures required to monitor the timeliness and accuracy of processing study forms. Mail from the Clinical Centers will be opened the same day it is received. Each form will be stamped with the date of receipt and the form will be electronically pre-inventoried, i.e. entered on a computer file of forms received. A second inventory of all patient records will be created

in the computer data base when the data from the forms are processed. These two inventories will be compared at regular intervals to identify discrepancies.

Forms are transferred to the data preparation area from the Coordination Office with a transmittal list identifying the study, the type of form, the number of forms and the date the batch was submitted. Each batch of forms received at the data preparation area is logged in on the same day it is received from the Coordination Office. Processing of the batch by the data entry operators can begin only after the batch has been logged in the system. The computer system can be used to track each batch and identify the current processing status of that group of forms. Further, it can be determined how much time is required to process each type of form.

All study forms are keyed independently by two operators. These two keyings are electronically compared, discrepancies are adjudicated whenever possible, and any remaining discrepancies are referred to the Clinical Centers. At the end of each comparison run, a list of all forms passing the comparison procedures (i.e., no discrepancies between keyings) is generated as well as a list of forms which failed this validation. This information will be used (a) to review the items which most frequently fail the edit to determine if the form should be redesigned or additional instructions given to the Clinical Center staff or data entry staff, and (b) to evaluate the performance of individual data entry operators.

After keying, all forms will be extensively edited and all corrections made at the Clinical Centers in response to edit messages will be posted. The validity of information on the computer master file will be ascertained by means of a forms audit; this is a structured procedure to compare the information on a sample of actual patient records with a printout of the record as recorded on the computer master file.

Printouts listing baseline and follow-up values for important study variables for individual patients, will also be generated, so that a site visitor to a Clinical Center may compare the printouts for selected patients against the original clinical records. At periodic intervals, lists generated from the computer files will be sent to each Clinical Center showing which forms and other materials have been received for the individual patients. The Clinical Centers will be asked to verify that these lists are accurate and complete.

The checking of custom designed analysis programs will be done primarily by preparing hand tabulations of the data for small subgroups of patients which have been selected either randomly or systematically. Various statistical methods will be used to detect potential outlier observations. All observations identified as outliers will be verified for correctness and if verified as correct, a decision will be made as to whether the value should be included in the data analysis.

12.4.3 Quality Control of Study Interpretations

Each $\dot{V}/\dot{Q}$ scan and angiography study will be interpreted locally at the Clinical Center where the patient is seen. However, to prevent bias inherent in knowledge of the patient, the official interpretation of a study will not be

based on the local interpretation, but rather on the interpretations of other study investigators. This independent grading by two investigators will also effect a reduction of the bias attributed to the interpretation of any particular investigator. Graders will be randomly selected by Data and Coordinating Center staff to further effect bias reduction. This approach also allows the Data and Coordinating Center to assess inter-observer variability of scan and angiogram readings.

In addition to the interpretations of the initial grader pair, the Data and Coordinating Center will select certain studies for further evaluation by the entire respective Working Group at scheduled meetings. Certain studies selected by Data and Coordinating Center staff will also be sent for re-interpretation to an original reader, without knowledge that he previously interpreted the study, in order to assess intra-observer variability.

12.4.4 Role of Consultants

Consultants, other than study investigators, and the NHLBI Project Office representatives will visit the Clinical Centers routinely, and when indicated on the basis of a center's performance. The objectives of these site visits are to assure training has been effective for PIOPED performance personnel, to assure equipment meets PIOPED specifications, and to verify procedures and data. Consultants will also be actively involved in the independent interpretation of $\dot{V}/\dot{Q}$ scan and angiographic studies, for the purpose of insuring accuracy of interpretation by regular graders.

CHAPTER 13

POLICY MATTERS

13.1 ADHERENCE TO PROTOCOL AND MINIMUM PATIENT LOAD

The ultimate success of the trial will depend upon absolute and rigid adherence to the protocol and Manual of Operations and the admission of sufficient numbers of patients to the study (a total of 150 patients for angiography) by each participating unit. Failure to adhere to the protocol, Manual of Operations, or the patient recruiting requirements will be reviewed by the Project Officer and the Policy and Data Safety Monitoring Board. Major infractions or suboptimal performance will result in termination of contract support.

13.2 ELIGIBILITY AND INCLUSION OF PATIENTS

It is of utmost importance that as little bias as possible be introduced into the selection of patients for inclusion in the trial. Therefore, patients with the criteria for inclusion (with no contraindications) who come to the attention of participating investigators, should be considered for admission to the study unless there is a lack of informed consent. The Principal Investigator is ultimately responsible for the necessary scheduling and coordination required for the follow-up examinations. If the patient dies during the follow-up period, the Principal Investigator will be expected to contact the patient's physician to obtain sufficient information to complete the data requirements and/or portmortem protocol.

13.3 INFORMED CONSENT

The policy of the Department of Health and Human Services stipulates that trials which involve human subjects must be preceded by assurance that the individual's safety, health, and welfare (including the rights of privacy) must not be infringed. Participation must be voluntary and the direct or potential benefits of the research must outweigh the inherent risks to the individual. Informed consent is difficult to define. Under the Department of Health and Human Services policy, the local institutions have the responsibility for protection of human rights with the guidelines provided by the Department.

A copy of the assurance of institutional compliance with this policy is required by the Project Office prior to the initiation of the study. This policy specifies that an informed consent must be obtained from all patients prior to entry into the trial.

Since it is recognized that this informed consent could introduce a bias into the study, considerable responsibility must rest with the physician seeking this consent. It has been suggested that informed consent may be "uneducated" consent. It may be possible, after an explanation with no coersion, to obtain a signature on a document that would satisfy the Institutional Review Board. The reality of the situation, however, is that it is the rare subject who appreciates all the ramifications of his entry into a study and the inconveniences and

risks involved. In fact, some of these risks may be truthfully unknown to the investigators. On the other hand, there is evidence to suggest that a too detailed exposition of all the pros and cons of the study design and the possible side effects can confuse the average subject to the extent that, in essence, the physician ends up making the decision for the subject. Hopefully, both extremes will be avoided in this study and consent will be both informed and as educated as possible.

It is impossible to provide a single statement that can be used by all physicians in all situations with all patients in this study. The form to be used by each institution must satisfy the local Institutional Review Board. However, the consent form used by each institution must include as a minimum the information contained in the consent form in Appendix VI.

13.4 REPORTING OF DATA

All data required by the protocol will be forwarded to the Data and Coordinating Center for storage, processing, and statistical analysis. All data will be forwarded to the Data and Coordinating Center within the agreed time schedule.

The Data and Coordinating Center will periodically distribute formal reports to DLD and the Clinical Centers. A final report will be prepared including a complete description of all study activities and an in-depth analysis of all data. Such an in-depth statistical analysis would include characterization of the study population, sensitivity and specificity of V/Q scans as compared to angiograms, and morbidity and mortality of the study population.

13.5 QUALITY CONTROL

The clinical and laboratory data will be collected and recorded by the personnel at participating Clinical Centers. All data will be forwarded to the Data and Coordinating Center within the agreed upon time schedule. Procedures to ensure that the data are accurate will be followed by the Clinical Centers and the Data and Coordinating Center and the External Review Consultants.

Rigorous control for the data collection and recording will be maintained by the Principal Investigator at each Center. The Principal Investigator or his designate at each Center will have the responsibility of scrutinizing the data and giving final approval before it is forwarded to the Data and Coordinating Center.

The Steering Committee and DLD will develop methods and schedules to assess and evaluate the accuracy of the data being collected in each Clinical Center to ensure an adequate level of data quality throughout the Centers. The Principal Investigator agrees to take whatever action necessary to maintain the accuracy and quality control determined by the Committee and DLD. To the extent possible, the Data and Coordinating Center will review all data submitted to the Center to ensure that it is free from errors and inconsistencies.

13.6 ANCILLARY STUDIES

Ancillary research studies may be conducted by the Clinical Centers if approved by the Steering Committee, Program Office, and the Policy and Data Safety Monitoring Board. These research studies are considered to be a resource for the total program. Individual investigators will have the opportunity, however, to separately publish the results of their ancillary research activities.

Ancillary studies involving patients can in no way interfere with the patient care prior to patient assignment or the subsequent diagnostic regimen. The purpose of this interdiction is to assure a homogeneous application of the study protocol to all patients.

13.7 STEERING COMMITTEE

The membership and duties of the Steering Committee are discussed in Chapter 11, Organizational Structure.

13.7.1 Officers

The officers of the Steering Committee are a Chairman, Co-Deputy Chairmen, and a Recording Secretary. The Chairman and Co-Deputy Chairmen will be of different professional disciplines and from different participating Clinical Centers. A member of the staff of the Data and Coordinating Center will serve as the Recording Secretary. The Chairman, in consultation with the Project Officer and the Data and Coordinating Center, will determine the agenda for the meeting. The Chairman will also preside over all the Steering Committee meetings and appoint members to ad hoc subcommittees. One of the Co-Deputy Chairmen shall serve in the absence of the Chairman. If, for any reason, the Chairman is unable to complete his term in office, the DLD will appoint a new Chairman. The Recording Secretary will record and distribute minutes of Committee meetings, notify members of meetings, keep and distribute protocols and other Committee documents, and maintain files of all Committee activities including files of scientific data.

13.7.2 Executive Committee

The Executive Committee is constituted of the Chairman, Co-Deputy Chairmen, the Director of the Data and Coordinating Center, and the DLD Project Officer. The Executive Committee is the governing body of the Steering Committee. It shall have general supervision of the affairs of the Steering Committee between meetings. The Executive Committee is subject to the order of the Steering Committee and none of its actions shall conflict with the actions taken by the Steering Committee.

13.7.3 Meeting of the Steering Committee

There will be a regular meeting of the Steering Committee not less than

twice a year. Five members of the Steering Committee constitute a quorum. The deliberations of the Steering Committee will be conducted in a parliamentary manner. Unless otherwise specified all decisions will be taken based on a simple majority of those present and voting, provided a quorum is established. The Steering Committee may act in meetings, by mail or by telephone, with written confirmation to the Chairman if voting is done by telephone. Special meetings of the Steering Committee shall be called by the Chairman, at the request of DLD, or at the written request of a majority of the members of the Steering Committee.

13.7.4 Consultants

The Steering Committee, with the concurrence of DLD, may invite as consultants individuals whom it feels would contribute useful information to the Steering Committee deliberations.

13.7.5 Voting

Each member has one vote concerning amendments to the protocol or on any other matters brought before the Steering Committee for a vote. Each individual appointed to a subcommittee, including consultants, will have one vote in subcommittee meetings.

13.7.6 Subcommittees

The Steering Committee may establish or abolish any subcommittee it determines to be in the study's best interest. The membership and the chairmanship of any subcommittee will be determined by the Chairman with the approval of the Steering Committee. No subcommittee may present a report outside the Steering Committee unless it has been specifically authorized to do so by the Steering Committee.

13.7.7 Data Analysis Subcommittee

This subcommittee will design necessary pretests in conjunction with other subcommittees. It will monitor the number of recruitments and make suggestions regarding methods for recruitment, follow-up and other matters which will help meet the objective of the study in more efficient ways. It will review proposals for ancillary studies and make recommendations to the Steering Committee regarding these proposals. It will develop plans for data analysis in collaboration with the Data and Coordinating Center.

This subcommittee will also deal with interpretations of diagnostic and endpoint criteria. It will periodically review these criteria and recommend changes, if required, to the Steering Committee.

13.7.8 Certification and Quality Control Subcommittee

This subcommittee will monitor the performance of the Clinical Centers and the Data and Coordinating Center and report findings to the Steering Committee. Within each center it will monitor the study organization and procedures, the maintenance of patient rosters, the adequacy of study personnel, and the methods and equipment being used in the study.

13.7.9 Publication and Presentation Subcommittee

This subcommittee will review all written and oral presentations on the design, progress and results of the study, including any ancillary studies. The subcommittee will, as a minimum, follow National Heart, Lung, and Blood Institute guidelines on presentations and publications.

13.8 PUBLICATIONS

The group will present or publish from time to time the results of studies subsequent to conclusion of data collection. Members and consultants are encouraged and urged to analyze and publish data based on the study, provided they adhere to the guidelines determined by the NHLBI. Approval for publications and presentations must also be granted by the Steering Committee or its delegated subcommittee.

The Chairman, with the approval of the Steering Committee, may designate and appoint members to a writing subcommittee for any study report. A writing subcommittee will be automatically discharged when it submits its final report.

There is likely to be a great variety of publication situations and degrees of appropriate acknowledgements for members and consultants, including the special requirements of some journals. Also, the interdisciplinary nature of the study requires that material intended for publication be reviewed by both representatives as well as appropriate advisors in other fields. Therefore, all papers for publication, abstracts, presentations at meetings, or other public distribution of results based on data for patients entered in the study must be sent to all members of the Publication and Presentation Subcommittee not less than two weeks prior to initial submission of the report. The subcommittee shall decide: (1) whether the scientific content of the paper and interpretation of the data are acceptable; (2) whether the contributions of members, representatives, and consultants are properly acknowledged; and (3) whether publication of the paper is in the best interest of the study. Each member of the subcommittee shall notify the Chairman of the subcommittee regarding his approval or disapproval of the report as submitted, with reasons for any disapproval and recommendations for changes. The subcommittee Chairman shall then notify the principal author of the majority decision of the subcommittee which may include approval, approval contingent upon specific revisions, approval with suggestions for revision and resubmission, or disapproval. In case the subcommittee does not reach a majority decision, the matter will be deferred for decision by the Steering Committee at its next meeting. Membership in the Steering Committee implies agreement to abide by

these procedures for all publication based study data. The decision of the Steering Committee may be appealed to the appropriate authority within the NHLBI. The authors shall abide by the final decision of the NHLBI. All inquiries from journals, magazines, radio stations, television stations, newspapers or societies are to be directed to the Branch Chief, Interstitial Lung Diseases Branch, Division of Lung Disease, NHLBI.

13.9 VETO

The Director, Division of Lung Diseases, NHLBI, is empowered to exercise a veto on any decision of the Steering Committee which he/she considers not in the interest of the study. The veto, if exercised, should be communicated in writing to the Chairman within 30 days of the Steering Committee decisions.

CHAPTER 14

ANCILLARY STUDIES

14.1 INTRODUCTION

The addition of ancillary studies to the PIOPED protocol at PIOPED Clinical Centers will be subject to Steering Committee review as described in Chapter 2 and in Chapter 13. PIOPED presents a remarkable opportunity to advance the study of thromboembolic disease because of the remarkable patient population to be collected. The PIOPED case series of angiogrammed patients with pulmonary embolism will be a large one. Since PIOPED's design will prospectively obtain estimates of $\dot{V}/\dot{Q}$ scan sensitivity and specificity, newer diagnostic techniques applied along with $\dot{V}/\dot{Q}$ scan can 1) have their own sensitivity and specificity estimated, 2) have their estimated sensitivity and specificity compared to the V/Q scan sensitivity and specificity estimated on the same patients, and, 3) be subject to pilot study easily and inexpensively prior to large scale study should an independent, full scale study be justified for a promising new technique. Biomedical questions may also be answered in the PIOPED patient population.

The following sections of Chapter 14 describe ancillary studies thus far proposed by the PIOPED investigators. In PIOPED, ancillary studies are any scientific investigations on PIOPED subjects not incorporated into the uniform PIOPED protocol for all six Clinical Centers. Ancillary studies must have financial support independent of the main study. The PIOPED Steering Committee will approve ancillary studies which it judges will not undermine the primary PIOPED objective, "to study prospectively the relative contributions of clinical assessment, laboratory tests and $\dot{V}/\dot{Q}$ scanning as compared to angiography and outcome in the diagnosis of acute pulmonary embolism." None of the following studies have as of yet been officially approved.

14.2 SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

Single photon emission computed tomography (SPECT) gives an accurate representation of radiopharmaceutical distribution in three dimensions (1,2). Several studies have used SPECT for imaging the distribution of pulmonary perfusion (3-7). In the comparison of SPECT and planar perfusion imaging, studies have shown defects present on the SPECT images which are not detected on the planar views (6). The characterization of segmental and nonsegmental defects is improved with SPECT and has improved the accuracy of the study in patients with suspected pulmonary embolism (4,5). The limitation of SPECT in evaluating patients with suspected pulmonary embolism is the difficulty in evaluating ventilation. Radioactive gases such as Xe-133 are unsatisfactory, since Xe-133 study requires a wash-in phase of three to five minutes and a wash-out phase. Thus, the continual changes in radiopharmaceutical distribution precludes accurate representation of the isotope from a camera rotation of approximately 20 minutes which is necessary to obtain the counts appropriate for a SPECT study. Ventilation studies with SPECT have been performed with Kr-81m (5), but the number of counts available during a short rotation limit the value of the study. The development of new Tc-99m-labeled aerosols for lung ventilation studies may make it feasible to use the aerosols for evaluating ventilation (6). However, the same radioisotope (Tc-99m) will be used for both the ventilation and perfusion study. By doing the perfusion study

first and storing the digitized images, and then performing the ventilation study, the perfusion study can be subtracted from the ventilation study after appropriate normalization.

This ancillary study proposes SPECT perfusion studies on approximately 50 patients during the first year of patient recruitment, and $\dot{V}/\dot{Q}$ SPECT studies during the second year of patient recruitment. During the first year, studies will be performed on patients having a routine $\dot{V}/\dot{Q}$ study performed during the normal work day. Perfusion SPECT study will be performed immediately after the planar imaging study. The perfusion SPECT study adds an additional 45 minutes in Nuclear Medicine which should not interfere with the overall purpose of PIOPED. The study will attempt to determine whether or not there is additional information obtained from the characterization of the perfusion abnormalities as determined by SPECT. If SPECT perfusion studies prove feasible, SPECT $\dot{V}/\dot{Q}$ studies will be performed during the second year of recruitment.

Proposing Institution(s): University of Pennsylvania

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14.3 DIGITAL SUBTRACTION ANGIOGRAPHY

Digital subtraction angiography (DSA) is a relatively new technique which provides an alternative to standard pulmonary angiography for the diagnosis of pulmonary embolism. Potential advantages of DSA include the ability to study

the pulmonary circulation without having to pass a catheter through the right ventricle and across the pulmonary valve and the potential for reduction of procedure time and radiation exposure. It also offers the possibility that invasive procedures such as selective pulmonary angiography may be performed with less contrast material.

Patients admitted to the PIOPED protocol who undergo pulmonary angiography will be candidates for DSA. Patients will be first studied by the standardized pulmonary angiography protocol. Only patients who have tolerated the pulmonary angiography well with stable vital signs and who have received less than 150 cc of contrast will be studied with DSA. The procedure will have been discussed with each patient prior to the initiation of pulmonary angiography with separate informed consent obtained.

Patient monitoring will continue throughout the procedure following the guidelines of the standard protocol. Patients first will undergo selective DSA with small doses (perhaps 5 ml of Renografin 76) injected directly into the pulmonary artery. The catheter will already have been inserted in the pulmonary artery so no additional manipulation of the catheter will be necessary.

The catheter will then be withdrawn from the main pulmonary artery into the right atrium. The field of view of the DSA device will be positioned over the main pulmonary artery. The patient will receive 30 cc of Renografin 76 at a rate of 20 ml per second. Images will be obtained beginning immediately before injection of contrast at a rate of three images per second for three seconds, followed by one image per second for four to six seconds. Following completion of the study, the catheter will be removed following the guidelines of the standard protocol. The guidelines for post-procedure patient care will be followed as also outlined in the angiographic protocol. The studies will be performed using a 12" field of view DSA system (Technicare Corporation, Solon, Ohio).

The DSA will be interpreted by the local institution performing the study. The same criteria will be used as for the conventional angiograms and the results recorded on a copy of the official angiographic interpretation form.

The results of DSA will be compared with the results of the standard pulmonary angiograms for calculation of the sensitivity, specificity and overall accuracy of the DSA.

Proposing Institution(s): Henry Ford Hospital

14.4 INDIUM-111 PLATELET SCINTIGRAPHY

PIOPED represents a unique opportunity to study a well defined patient population in the clinical setting of a suspected pulmonary embolus with indium-111 platelet scintigraphy. The concurrent acquisition of venography, ventilation-perfusion scintigraphy and pulmonary angiography will allow comparative studies both for the diagnosis of deep vein thrombosis and pulmonary embolism.

Preliminary studies involving platelet scintigraphy have correlated

extremely well with venography (sensitivity 91%; specificity 95%), have produced accurate diagnosis within 4 hours of injection of the isotope and have demonstrated potential application in monitoring therapy for up to 5-7 days (1-6).

Questions that will be addressed in this ancillary study include: 1) identification of the source of pulmonary emboli; 2) the accuracy of platelet scintigraphy versus venography in the diagnosis of venous thrombosis and the specificity, versus angiography, in pulmonary embolism; 3) the efficacy of therapy in the acute phase; 4) the incidence of post-venogram thrombophlebitis; and 5) the proportion of patients suspected of suffering from pulmonary embolism with pulmonary angiograms negative for emboli and leg venograms positive for thrombi. Indium-111 platelet scintigraphy has been added without altering any element of the main protocol.

Blood will be drawn for platelet labeling as soon as possible and labeled platelets reinjected immediately following the lung scan. The preparation of the labeled platelets will take approximately 90 minutes. Following injection of the platelet suspension, the chest and lower limbs will be imaged within 4 hours. Imaging of the lower limb will consist of 10 minute images using both photo peaks of Indium-111 with a symmetric 20% window. Careful attention will be paid to spatial registration of the two photopeaks. Imaging of the calves, thighs, and lower abdomen and pelvis will be obtained using a wide field of view (WFOV) gamma scintillation camera. Careful note will be made of subcutaneous hematoma, superficial thrombopheblitis, inflammatory joint disease or any other pathology involving the limb. Following imaging of the lower limbs, 5 minute views of the chest (anterior, posterior, and posterior oblique views) will be performed. Only the 247 keV photopeak of Indium-111 in will be used, to avoid crossover contamination from ^{99}Tc present in the lungs from the perfusion scintigram, during the first 24 hours of imaging. The second set of platelet images will be performed prior to, and the third set 24-48 hours after the lower limb venogram. If any platelet images are considered positive, sequential platelet images will be obtained on at least alternate days for 5-7 days.

Data analysis will consist of: 1) initial interpretation by the investigators conducting the study on-site; 2) blinded interpretation of platelet images from each institution by 2 readers from the other participating institutions.

This study will be performed under IND No. 21052, under which a maximum of 500 microcurries of Indium-111 is allowed per study. The dose of Indium-111 in this protocol will be adjusted in order to remain within the limit of 5 rads to any organ (3 rads to bone marrow). The critical organ in this case is the spleen, which receives approximately 1 rem per 50 μCi of Indium-111 platelets injected. Doses to other tissues are substantially less, with reported estimates (per mCi of Indium-111) as follows: 0.6-4.2 rem to the liver; 0.5-1.0 rem to the bone marrow; 0.1-0.8 rem to the gonads; and 0.3-0.9 rem to the whole body (7-9).

Leg venography will be performed on selected patients following ventilation-perfusion scanning and pulmonary angiography. This ancillary study will be undertaken only in those centers which will be performing Indium-111 labeled platelet scans of the lower extremities. It is estimated that 50 patients will undergo peripheral venography each year in each of the appropriate institutions.

Peripheral venography will be performed within 24 hours following completion of the pulmonary arteriogram. Since the Indium-111 platelet scans will be performed at the time of the ventilation-perfusion scans, this will assure that peripheral venography will be performed within 48 hours of the time of the platelet scanning. This time frame should prevent the introduction of a significant number of false positive or false negative correlations with the Indium-111 platelet scanning. Although occasionally the peripheral venography may be performed on the same day as the pulmonary angiogram, this is generally impracticable. It is generally prudent to limit the number of contrast studies performed in any one day. Allowing a period of overnight hydration should avoid the risk of compromising renal function with the additional contrast load.

All patients considered for leg venography must have undergone Indium-111 labeled platelet scanning of the legs at the time of the ventilation-perfusion scan. Only patients whose ventilation-perfusion scans are interpreted as showing a high or intermediate probability of a pulmonary embolism will be considered. Only patients whose pulmonary arteriograms have shown no evidence of pulmonary emboli will be recruited. Patients must be deemed suitable for this ancillary study by the referring clinical scientist.

Patients whose ventilation-perfusion scan is normal or shows a low probability for pulmonary embolism will be excluded from this study. Patients with evidence of pulmonary embolism on the pulmonary angiogram will be excluded. Patients with severe peripheral vascular disease, especially those patients with diabetic vascular disease, will be excluded since peripheral venography carries an increased risk in this subgroup. Patients who are less than 18 years of age, pregnant, in severe renal failure, in severe shock, or who have a proven contrast allergy will be excluded.

If either of the legs is symptomatic, the more symptomatic will be selected for the initial venogram. If both lower limbs are asymptomatic, the side which was punctured for the pulmonary angiogram will be selected first.

Contrast material will be introduced by rapid hand injection while there is continuous observation of the injection site by the angiographer. Most of the studies will be obtained without the use of compressive tourniquets. If there are extensive varicosities or if the initial films are unsatisfactory because of excessive shunting of contrast through the superficial venous system, tourniquets will be applied at the discretion of the angiographer. Although varying somewhat with individual patients, radiographic factors will be approximately as follows: calf - 70 kVP @ 20 MAS, knee - 70 kVP @ 32 MAS, thigh - 70 kVP @ 40 MAS, pelvis - 85-95 kVP @ 50-90 MAS. If the initial films are not diagnostic, additional overhead films may be taken or fluoroscopic spot films will be taken of the areas in question. Forty-three percent iothalamate meglumine will be used as the contrast agent. Approximately 100 ml of contrast will be used to examine each extremity. If additional spot films are required, a total of 150 ml of contrast may be used in each limb.

If clot is identified in any of the veins of the examined limb, the study will be terminated. If no clot is identified by any of the criteria listed below, the contralateral leg will then be examined with the same technique. No more than a total of 300 ml of 43% radiographic

contrast will be used for the venographic examination in any patient.

Criteria for diagnosing deep venous thrombosis will be those outlined by Rabinov and Paulin (10). In order of decreasing certainty, the signs are: first, constant, sharply outlined filling defect; second, abrupt termination of the contrast column with a meniscus sign; third, nonfilling of part or all of the deep venous system; and fourth, extensive collateral flow (i.e., diversion of normal flow pattern).

Proposing Institutions: Duke University
University of Pennsylvania
Yale University

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14.5 NUCLEAR MAGNETIC RESONANCE

Nuclear Magnetic Resonance (NMR) appears to have considerable potential in the diagnosis of pulmonary embolism. It has been shown in vitro that clotted blood has different NMR characteristics from flowing blood (1). Rapidly flowing blood produces a different NMR signal than does stagnant or slowly flowing blood (2). Experimentally produced pulmonary emboli have already been demonstrated successfully in dogs using NMR (3), and a few humans have also been successfully studied (4). The sensitivity and specificity of NMR are undetermined.

Ideally, we would like to expand NMR to all six Clinical Centers. All six institutions involved in the study either have NMR imaging capabilities at the present time or will have by the end of 1984. However, because of the considerable clinical and experimental demands placed on NMR facilities, it would be unrealistic to expect that all patients in this protocol could obtain an NMR examination within a specified time frame following the isotopic and angiographic studies. NMR examinations of very seriously ill patients and particularly those patients requiring monitoring equipment is difficult and, at times, contraindicated. In the current stage of NMR imaging technology, different groups have different equipment and use different pulse sequences. There is considerable variation in magnets, hardware, software, and other NMR parameters. It would be premature to specify standard NMR to be used by all participating centers.

For these reasons, NMR will be omitted from the universal protocol, but will be performed in as many patients in this study as is feasible by all six participating institutions as an ancillary study. Every attempt will be made to complete the NMR imaging examination within 24 hours of the isotope scan.

NMR Equipment

1) Duke University - 1.5 T superconductive unit - operational

2) Henry Ford Hospital - 1.9 T superconductive - operational

3) Massachusetts General Hospital - .6 T superconductive - operational

4) University of Michigan - .35 T superconductive

5) University of Pennsylvania - .12 T resistive - operational
   (1.5 T superconductive later in 1984)

6) Yale University - .15 T resistive - operational
   (1.5 T superconductive late 1984 or early 1985)

Proposing Institution(s): Duke University
Henry Ford Hospital
Massachusetts General Hospital
University of Michigan
University of Pennsylvania
Yale University

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14.6 VENOGRAPHY AND IMPEDANCE PLETHYSMOGRAPHY

One alternative strategy to diagnose pulmonary embolism is to search for peripheral sources of emboli. Several autopsy series conclude that pulmonary emboli arise largely from proximal deep vein thrombosis in the femoral or iliac veins or in the vena cava (1-3). Distal vein thrombosis (below the popliteal vein) is a less common source of pulmonary emboli (4). In deep venous thrombosis, the leg venogram is the standard diagnostic test.

The most sensitive and specific noninvasive test to detect proximal deep venous thrombosis is impedance plethysmography (IPG). In patients suspected of deep venous thrombosis compared to contrast venography, the sensitivity of this examination is 93% (5,6). In patients suspected of pulmonary emboli, the specificity of IPG compared to contrast venography in detecting proximal deep venous thrombosis is 86% (7).

Recently Hull et al have reported that approximately 30% of their patients with abnormal lung scans and negative pulmonary angiograms had deep vein thrombosis on leg venography (8). PIOPED offers an opportunity to confirm or refute the impression Hull's work gives. In those patients with pulmonary angiography negative for pulmonary embolism, an IPG will be performed. A positive IPG suggests the presence of proximal deep vein thrombosis and would be followed with bilateral leg venography for confirmation.

A high prevalence of proximal deep vein thrombosis in angiogram negative patients may support the diagnostic strategy of performing an IPG as a screening study in all patients with an abnormal lung scan, and confirming an IPG positive for deep vein thrombosis with leg venography. Some physicians may prefer these diagnostic tests to pulmonary angiography.

This ancillary study will also determine whether or not IPG adds to the clinician's decision whether or not to treat with anticoagulants. Positive IPG confirmed by leg venography adds to the clinician's indication for anticoagulation. Since sensitivity and specificity cannot be estimated without leg venography follow-up of IPG negative patients, this study will not be a part of the main protocol extending to all centers.

Proposing Institution(s): University of Pennsylvania

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14.7 HEMODYNAMIC STUDIES

Acute pulmonary emboli are associated with obstruction of a portion of the pulmonary vascular bed. One of the major unresolved issues in the treatment of pulmonary emboli is the extent of recovery of these derangements and whether or not there is a significant difference in the degree of this recovery when heparin (which prevents clot propagation) is compared to streptokinase (which promotes fibrinolysis). Persistent post-embolic pulmonary hypertension may be related to recurrent embolic events and not a sequel of the initial event (1).

Patients who are initially angiogramed will have resting pulmonary hemodynamics and cardiac indices measured. While treatment for pulmonary embolism will not be standardized, some patients may receive thrombolytic therapy. During long-term follow-up (i.e., 6-12 months) patients with previously documented pulmonary embolism will be restudied by balloon flotation right heart catheterization to evaluate pulmonary hemodynamics both at rest and during exercise. This will document the course of resolution of pulmonary vascular impairment, and may open the question of whether or not thrombolytic therapy has a long-term benefit in the treatment of pulmonary embolism.

Proposing Institution(s): University of Pennsylvania

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14.8 HEPARIN PHARMACOKINETICS

The objective of this ancillary study is to characterize the pharmacokinetics of heparin in the clinical setting. The rationale is that better understanding of its clinical pharmacology will lead to better use.

Patients accepting this ancillary study will be in-patients who have been diagnosed as having deep vein thrombosis and/or pulmonary embolism and will be receiving heparin by intravenous infusion for therapeutic purposes. Prior to the initiation of heparin therapy, a venous blood sample will be collected for the determination of the in vitro relationships between the anticoagulant effect (APTT) and added heparin and also between the neutralizing amounts of polybrene and added heparin. Heparin activity in plasma samples collected during heparin administration will be determined based on these relationships. Several plasma constituents which may be determinants of the in vitro relationships will be determined. These include antithrombin III and other serine protease inhibitor Following the initial intravenous bolus injection of heparin, 4-5 blood samples will be collected over the next 1 1/2-2 hours for heparin determination, at which time the continuous intravenous infusion of heparin is started. These samples will allow the calculation of the pharmacokinetic parameters of heparin after a single dose, including biologic half-life, apparent volume of distribution, and total clearance. During the continuous intravenous infusion of heparin, two blood samples will be collected each day for heparin determination. These samples will allow daily calculations of total clearance. Following the discontinuation of heparin infusion, five blood samples will be collected over 2-5 hours for heparin determination. When all heparin has been eliminated, a blood sample will be collected again for the determination of the in vitro relationships between the anticoagulant effect and added heparin, and also for the determination of those plasma constituents which may be determinants of these relationships. The post-infusion samples will allow the calculations of total clearance of the post-infusion biologic half-life, which will be compared to that obtained after the initial dose.

The only risks to the patients associated with participating in this study are those of localized bleeding at venipuncture sites due to withdrawal of blood samples. This risk will be minimized by collecting blood samples through indwelling intravenous catheters. Total blood loss due to the study is about 100-150 ml over the course of hospital stay. There will not be direct benefits to the patients for participating in this study, except for more frequent monitoring of the anticoagulant effect of heparin. The potential benefit to society to be gained as a result of this proposed work is efficacious and safe

use of heparin (1). All the necessary laboratory facilities for this study are available in the Division of Clinical Pharmacology. This study will be supported by NIH grant No. HL-24343.

Proposing Institution(s): Duke University

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14.9 KETANSERIN

Pulmonary emboli are associated with a variety of hemodynamic and gas exchange consequences, some of which have been attributed to serotonin. Ketanserin is a drug which antagonizes serotonin-induced vasoconstriction and bronchoconstriction and platelet aggregation. In experimental animal pulmonary hypertension, Ketanserin has reversed a large part of the induced hypoxemia (i.e., normalized physiologic shunt) without effecting physiologic dead space.

Selected patients with pulmonary embolism will have determination of V_D/V_T, shunt fraction, pulmonary artery pressures and cardiac indices before and after the acute infusion of Ketanserin. Ketanserin does slightly prolong the bleeding time by interfering with platelet aggregation. This will need to be considered in managing anticoagulation of patients with pulmonary embolism. A protocol for following these patients, probably including template bleeding times will be established.

Proposing Institution(s): University of Pennsylvania

14.10 XENON-127 VENTILATION STUDY

With Xenon-127 (Xe-127) the ventilation scan may follow the perfusion scan. With Xe-133 every patient must have a ventilation scan before perfusion scan (1,2). Thus, with Xe-127 some patients may be able to avoid the radiation dose associated with a ventilation scan. Also, the energy of the Xe-127 is more properly suited to the Anger camera. Thus, the resolution of the images is improved with Xe-127 and is comparable to that obtained with perfusion scans.

To study both Xe-133 and Xe-127 PIOPED patients will receive a Xe-133 scan as specified in the main protocol, a 99m-Tc MAA perfusion scan as specified in the main protocol, and a Xe-127 ventilation study obtained from the projection deemed most appropriate on the perfusion scan. If the perfusion scan is normal, the Xe-127 scan will not be performed. All patients with abnormal perfusion scans will undergo pulmonary angiography and the results will be compared with those found on both scans. The University of Pennsylvania has used Xe-127 for ventilation studies for 14 months.

Proposing Institution(s): University of Pennsylvania

REFERENCES

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14.11 SUMMARY

Within the PIOPED design, a number of sophisticated University Medical Centers are prepared to bring new techniques to bear on the problems of pulmonary embolism, at the same time as providing the scientific foundation for evaluating currently used techniques which have remained controversial because of inadequate, quantitative evaluation in the past.

APPENDIX I

LIST OF DATA COLLECTION FORMS