STUDY PROTOCOL

OF THE

PATIENT REGISTRY

FOR

THE CHARACTERIZATION OF

PRIMARY PULMONARY HYPERTENSION

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1. Introductory Summary

This protocol describes the essential aspects of the Patient Registry for the Characterization of Primary Pulmonary Hypertension (PRCPPH), a collaborative study of the natural history, pathogenesis, etiology and treatment of Primary Pulmonary Hypertension. This observational cohort study will involve the participation of 37 Clinical Centers which will follow approximately 500 patients over a period of 1 to 3 years. Data on first order relatives of patients will also be included in the Registry. Therapeutic interventions will be recorded and will be included in the analysis of the data obtained from this study. A Manual of Operations and Procedures will be developed which will specify in detail the operations and procedures needed for the conduct of this study.

2. Background

Primary Pulmonary Hypertension (PPH) is a term currently used to define the presence of pulmonary hypertension of unexplained etiology. Although the disease entity was recognized in the early 1900's (1), it was only since 1951 that Dresdale coined the term primary pulmonary hypertension (2) which is used today.

In order to make the diagnosis of primary pulmonary hypertension, positive and negative clinical criteria must be met. There must be clinical evidence of pulmonary hypertension, usually supported by the physical examination, chest x-ray, and electrocardiogram, but documented by an elevation of pulmonary artery pressure on cardiac catheterization. Equally important is the exclusion of any other recognizable cause for the pulmonary hypertension. The diseases most often excluded are chronic obstructive pulmonary disease (COPD), congenital heart disease, mitral stenosis, left ventricular dysfunction, and recurrent pulmonary emboli. Some investigators who have been very aggressive in the evaluation of patients with suspected PPH have been able to detect occult diseases that are then presumed to be the cause of the pulmonary hypertension (3).

Thus, clinical diagnosis of primary pulmonary hypertension, being a diagnosis of exclusion, is only as reliable as the extent to which secondary causes for pulmonary hypertension have been ruled out. Unfortunately, the literature contains several studies on patients with a presumed diagnosis of PPH in which the criteria for the diagnosis are not given.

There have been attempts to define PPH by the histologic changes seen in the pulmonary vasculature on biopsy. In 1973, the World Health Organization agreed on three histologic patterns consistent with Clinical PPH (4): namely, plexogenic pulmonary arteriopathy, recurrent pulmonary thromboembolism, and pulmonary venoocclusive disease.

Plexogenic pulmonary arteriopathy is a term used to describe the changes manifest by concentric intimal fibrosis, necrotizing arteritis, and plexiform lesions. Plexiform lesions, although felt to be specific for vasoconstrictive primary pulmonary hypertension, have now been shown to be present in pulmonary hypertension from diverse causes (5).

Recurrent pulmonary thromboembolism is the second category of histologic patterns felt to be compatible with the clinical disgnosis of PPH. This subgroup applies to patients who had multiple recurrent microembolization to their lungs which were clinically silent except for the cumulative effect in producing pulmonary hypertension. Microscopic examination of the pulmonary vasculature in these patients reveals microembolization to be the predominant pattern. Evidence for some degree of thromboembolization, however, is found in most patients dying of pulmonary hypertension (6,7).

Pulmonary veno-occlusive disease, a very uncommon entity usually affecting children, is the third category of histologic patterns felt to be compatible with clinical PPH. This disease is distinctive histologically by the changes which are predominantly seen in the pulmonary veins and venules (8). Occasionally this diagnosis can be made antemortem by noting an elevated pulmonary angiographic pattern (9).

Thus, it currently appears that there is no distinctive histological pattern that allows separation of primary pulmonary hypertension from other diseases that can secondarily produce pulmonary hypertension as well. As with the clinical diagnosis of PPH, the pathologic diagnosis of PPH becomes one of exclusion as well.

The variety of clinical presentations of PPH, as well as the different histologic changes noted now raises the question as to whether PPH is a single disease entity or a heterogeneous group of diseases with a common manifestation. Open lung biopsies on these patients have occasionally uncovered an unsuspected disease process (3). Unfortunately, since open lung biopsies have not been routinely performed on these patients, there is no way of knowing what diseases have been included in our current definitions of PPH.

2.1 Epidemiology

Although there are less than 1000 reported cases of PPH in the literature, there do appear to be some recognizable patterns in the appearance of the illness. The overall incidence in the general population is unknown but the disease is found at autopsy in approximately 1% of all patients having cor pulmonale (10). There appears to be a bimodal distribution among patients with PPH regarding age of onset characterized by an early peak in infancy with males and females equally affected (11), and another peak in the third and fourth decades with a female to male predominance of approximately 4:1. No predilection towards any specific race has been described. Geographical areas with high incidences have also not been found and, with the exception of the

increased incidence in Europe following the introduction of the drug aminorex (discussed below), no particular environmental exposure has been associated with PPH.

Familial aggregation has been well documented with affected twins, siblings, and offspring being reported (12-14). The exact mode of inheritance has not been clearly defined, as no mention of testing for the disease in families is reported in most series. Therefore the role of genetic transmission of the illness remains to be studied.

2.2 Natural History

The natural history of PPH remains undefined. There appears to be two types of affected patients; one group whose clincical course declines rapidly from the time of diagnosis, with an average survival of 2-3 years, and a second group that maintains an indolent course with the level of pulmonary hypertension and clinical symptoms remaining constant for 15-20 years (15). Follow-up on most series of reported cases is limited however, and the true natural history of the disease(s) needs clarification. If the two sub-groups mentioned are in fact a reality, then it would be important to look for any features that would enable investigators to distinguish into which sub-group a particular patient falls.

We have constructed a life table below based on 41 cases of PPH collected by Voelkel and Reeves (68):

Years after onset	Number alive at beginning of interval	Number dying in interval	Estimated Life Table probability of surviving from onset to end interval
(X)	l_x	d_x	p_x
0-1	41	10	.72
1-5	31	18	.13
5-10	13	4	.08
10-15	9	3	.05
15-20	6	4	.00

This specific data indicates that long term survival is poor; median survival is approximately 3.4 years; only 13% survived 5 or more years.

Spontaneous regression of the disease has also been reported (16), but appears to be extremely rare. Long term survival has not been correlated to the level of pulmonary hypertension at the time of diagnosis, but rather to the cardiac index (17). A recent retrospective study has also suggested improved survival with anticoagulant therapy and the presence of a right-to-left shunt via a patent foramen ovale (18).

2.3 Etiology

No known etiologic factor has been consistently incriminated in PPH. Several associated diseases have led, however, to the possibility that some definable causative factors exist. The association of pulmonary hypertension with advanced liver disease is well established (19) and raises the question

as to whether vasoactive compounds that may bypass liver degradation in these patients can stimulate the pulmonary vasculature. Congenital heart disease associated with left-to-right shunts often produce pulmonary hypertension, believed to be related to the increased pulmonary blood flow and pressures transmitted to the pulmonary circuit (20). Severe pulmonary hypertension is usually confined to post-tricuspid level shunts, with pulmonary hypertension being uncommon from shunts at the pre-tricuspid level (i.e. anomalous pulmonary venous draining) (21). On occasion, however, patients with atrial septal defects have been known to develop progressive, persistent pulmonary hypertension following the closure of the shunt (21). As increased pulmonary blood flow has been shown to stimulate hypertrophy of pulmonary vascular smooth muscle, (22), the question is raised as to whether increased pulmonary blood flow can trigger pulmonary hypertension.

There is also an association of pulmonary hypertension with the collagen vascular diseases. This is often seen in patients with minimal clinical manifestations of the collagen vascular diseases (23-26). Vasculitis has been the presumed reason these patients develop pulmonary hypertension, but good pathologic correlations are lacking. Almost all of the collagen vascular diseases, i.e., SLE, scleroderma, rheumatoid arthritis, mixed connective tissue disease, etc., have been associated with pulmonary hypertension in some patients.

Vasospasm has also been implicated as a possible causative factor in PPH, due to frequent association with Raynaud's phenomena (27). Associations with

other vasospastic type disorders, such as migraine or variant angina have not been made.

Recurrent thromboembolism, besides being implicated as a separate cause of primary pulmonary hypertension, has also been associated with plexogenic pulmonary arteriopathy (11). Diffuse microembolism has been felt to cause pulmonary hypertension by physically reducing the cross-sectional area of the pulmonary bed (28). Recent investigations seem to suggest that vasoconstriction also occurs from pulmonary embolism by the liberation of prostaglandin-like substances from platelets and surrounding vessels (29). As some degree of thromboembolism or thrombus in situ is seen in most patients dying from PPH, (6,7) the question is now raised as to whether this phenomenon is obligatory for the development of chronic pulmonary hypertension.

Although drug intake or diet was not recognized initially as having any influence on the development of PPH, an epidemic of PPH appeared in Switzerland, Austria and West Germany during the period 1967-70, following the marketing of the appetite suppressant drug, aminorex fumarate (30). The risk of developing PPH in patients taking this drug was about 2 percent, and appeared dose related (31,33). In addition, reports of regression of the disease have been noted in a few patients in whom the drug was discontinued (34). The drug aminorex is chemically related to epinephrine and amphetamine, and again raises the possibility that vasoactive compounds may play a role in the etiology of PPH. There are, however, some inconsistencies in the implication of aminorex as the causative agent in these people. Investigators

have been unable to produce pulmonary hypertension in any experimental animal fed aminorex in efforts to verify a cause and effect relationship.

2.4 Pathogenesis

The pathogenesis of PPH is unknown and will probably remain so until it is clarified as to whether the disease is or is not a single entity. The most often proposed mechanism for the illness has been primary vasoconstriction, as originally suggested by Wood (35). This theory is based on the appearance of marked medical hypertrophy of the pulmonary arterioles seen on biopsy of the lungs, which is felt to represent active vasoconstriction. This mechanism would be consistent with the associations made with patients who have pulmonary hypertension from suspected etiologic causes as closure of a left-to-right cardiac shunt, advanced liver disease where vasoactive compounds can bypass the liver and affect the pulmonary circulation, suspected liberation of vasoconstrictive substances from platelets during thromboembolism, and the ingestion of the amphetamine-like drugs such as aminorex. Because of the lack of a specific pulmonary vasodilator agent, this theory has been neither confirmed nor refuted with current data.

Autoimmune phenomena have also been invoked as a possible mechanism for PPH (36). The frequent appearance of a necrotizing arteritis on biopsy would support this theory, and would be consistent with the clinical associations made with the collagen vascular disorders, and possibly even with the familial patterns of inheritance occasionally observed. Although a limited clinical

trial on the use of the steroids and immuran failed to achieve therapeutic results in patients (37), this theory still remains untested.

Recent thromboembolism has also been proposed as one mechanism explaining PPH (38) although it is unclear whether the appearance of clots in the pulmonary circulation represents miliary embolization of thrombosis in situ. Most pathologists believe that thromboembolism alone could not account for the diffuse vascular changes that occur in PPH, but it remains possible that some element of thromboembolism is a necessary component of the disease process. Reports of improved longevity in patients receiving anticoagulants would lend support of this theory (18).

2.5 Clinical Features

For the most part, the elevation of pulmonary artery pressure per se produces no symptoms, as parallelled by patients with systemic hypertension, and is one reason why patients seem to present clinically with long standing pulmonary hypertension before recognizable clinical features develop. The clinical features that account for most of the patients' symptoms are usually either secondary to the increased pulmonary vascular resistance that limits pulmonary blood flow and thus causes symptoms of low cardiac output, (e.g., syncope, fatigue), or secondary to right heart failure from chronic pressure overload causing venous congestion. There are no clinical features that have as yet been identified that are specific for primary pulmonary hypertension. The major reason that early detection of PPH has not been forthcoming has been the lack of a non-invasive means of

measuring pulmonary artery pressure. Laboratory tests are often supportive of the diagnosis, but no knowledge exists about sensitivity or specificity of changes in ECG, chest x-ray, echocardiography or nuclear angiography with regard to PPH. Exercise tolerance tests have also not been studied as to their ability to identify patients according to severity of the disease, or indicate long term prognosis. Lung scanning is also a valuable test, which not only will identify patients with pulmonary emboli, but also will give information about changes in the distribution of the pulmonary circulation over time in affected patients. Again, no data on the diagnostic sensitivity and specificity of this technique are available.

2.6 Therapy

One of the main areas of controversy and confusion regarding PPH is what role, if any, does medical therapy have in altering the natural history of the disease. The natural history of the illness has not been clearly defined, mainly because of the scarcity of the illness. For this reason, controlled studies to evaluate drug therapy will be very difficult. Currently, our knowledge about the influence of drugs in these patients comes mostly from isolated case reports or small series with limited follow-up.

Medical therapy for PPH has two basic approaches in the hope of improving long term survival: prophylactic anticoagulation, and vasodilator therapy to reverse symptoms and the amount of pulmonary hypertension.

2.7 Anticoagulant therapy

Although the use of anticoagulants has been long recommended to

treat patients with PPH, regression of the disease in these patients has never been demonstrated to occur from anticoagulant therapy (39). Because the illness may have a prolonged and protracted course it is often difficult to assess if the disease process can be halted. The presence of some degree of thromboembolism in the pulmonary vasculature of a majority of patients dying from PPH has been used as the empirical rationale for therapy. Most investigators reserve the use of anticoagulants for patients with either suspected clinical thromboembolism, or with venous congestion from right heart failure where the incidence of deep vein thrombosis becomes increased (40). For obvious reasons, a small pulmonary embolism which might have no ill effect on a normal patient can have catastrophic consequences in a patient with PPH. One recent retrospective study done of the survival of patients with PPH suggested that prophylatic anticoagulation might have some benefit (18).

2.8 Vasodilator therapy

The recent advances in vasodilator therapy in the treatment of essential hypertension has stimulated renewed interest in the use of these agents in patients with PPH. Favorable responses to vasodilator drugs have been reported since 1954 (41); however most are are acute studies in isolated patients. Since the number of published reports on the use of vasodilator drugs in patients with PPH is few, one has to believe that favorable results from drug challenges are exceptionally uncommon. We have recently reviewed the literature regarding all published reports on the use of vasodilator agents in patients with PPH (41), and abstracted the data from those studies

that provided, as a minimum, measurements on the acute or short term effects of the drugs on the cardiac output, pulmonary artery pressure, and pulmonary and systemic vascular resistances, both at control and after thereapy. Since 1951, there have been only 13 such published papers, which describe the effects of 7 different drugs on 33 different patients (37, 41, 43-53). Eight of these were case reports, and one dealt with only two patients. Most studies dealt with the effects of one drug on one or more patients. Two studies dealt with the effects of two drugs on a single patient. Thus, there exists hemodynamic information about the results of 35 drug challenges in 33 patients with PPH in the current literature, and this information has been compiled in Table 2.1. The most often tested agents have been diazoxide and isoproterenol.

The conclusions made in the literature about the benefits of these drugs are often confusing. Successful therapy has been stated to be manifest by a reduction in the pulmonary artery pressure (35). This occurred in only 21 of the 35 trials included in Table 2.1, and the mean reduction of 3.01 mm Hg in pulmonary artery pressure was not significantly different from zero ($p<.10$). More recently, however investigators have used a fall in the calculated pulmonary vascular resistance as an indication of beneficial drug therapy (44,46,47,51). Besides the theoretical objections against using the pulmonary vascular resistance as a parameter for therapy (33), there are reports where the patients' pulmonary artery pressure was increased with drug therapy, yet the investigator concluded the drug was beneficial because the pulmonary resistance fell (46,47).

We reviewed the effects of these drugs on patients with PPH as reported and found some heretofore unrecognized drug effects. First, all of the vasodilator drugs caused the cardiac output to increase in all patients studied, regardless of the severity of the underlying pulmonary hypertension, with a mean increase of 1.96 liters/minute. Secondly, the pulmonary vascular resistance, and the systemic vascular resistance were reduced in every case as well. When we looked at the relative effects of these drugs on the systemic and pulmonary circulations, we found that, in approximately 70% of the cases in Table 2.1., the systemic vascular resistance was reduced to a greater degree than the pulmonary vascular resistance. However, in every case that the pulmonary vascular resistance was reduced more than the systemic vascular resistance, the pulmonary artery pressure was lowered as well, whereas it was lowered in only 35% of the cases in which the systemic vascular resistance was reduced more than the pulmonary vascular resistance ($p < .002$). The implications appear to be that in most cases, vasodilator drugs work predominantly on the systemic circulation, and that the calculated increases in pulmonary blood flow and reductions in pulmonary resistance that result are consequential. However, in selected cases, these agents appear to have a predominant effect on the pulmonary circulation which is not only manifest by a reduced pulmonary resistance, but by a fall in pulmonary artery pressure as well.

HEMODYNAMIC EFFECTS OF VASODILATOR DRUGS IN PATIENTS WITH PRIMARY PULMONARY HYPERTENSION AS REPORTED IN THE LITERATURE

Patient number	Dose	Cardiac output (L/min)		Mean systemic pressure (mmHg)		Mean pulmonary pressure (mmHg)		% fall in systemic resistance	% fall in pulmonary resistance
		before	after	before	after	before	after		
ACETYLCHOLINE (i.v. infusion)									
1	0.5 mg/min	4.7	5.2	122	130	74	35	4	60
2	4.25 ug/min	1.72	1.87*	101	96	39	30	13	30
3	3 ug/min	4.19	5.05	62	64	82	88	15	11
TOLAZOLINE (i.v.)									
3	75 mg	3.44	4.18	72	68	82	80	26	22
4	25 mg	2.72	3.85	95	93	48	35	31	50
5	50 mg	3.53	5.85	102	106	47	46	37	41
6	10 mg	6.7	8.0	100	98	52	45	18	34
7	50 mg	3.73	4.98*	85	81	72	68	28	29
ISOPROTERENOL (i.v. infusion)									
8	1 ug/min	3.1	4.8	83	82	53	50	36	67
9	2 ug/min	3.6	5.1	90	92	56	60	28	24
10	2 ug/min	2.5	3.5	127	118	90	110	43	12
11	1 ug/min	3.6	4.4	88	84	40	45	22	11
12	1 ug/min	2.2	3.4	86	82	68	80	38	23
13	1 ug/min	3.2	5.0	82	72	64	85	45	13
14	2 ug/min	2.1	3.2	99	118	57	80	22	8

Table 2 (cont'd)

Patient number	Dose	Cardiac output (L/min)		Mean systemic pressure (mmHg)		Mean pulmonary pressure (mmHg)		% fall in systemic resistance	% fall in pulmonary resistance
		before	after	before	after	before	after		
YDRALAZINE (oral)									
15	50 mg	3.5	8.6	135	110	78	47	67	76
16	50 mg	3.3	5.4	110	102	56	34	43	63
17	50 mg	4.9	8.8	110	110	68	75	44	40
18	50 mg	3.6	5.6	76	80	61	60	34	37
IAZOXIDE (i.v.)									
19	300 mg	4.1	5.6	82	73	73	70	53	30
20	300 mg	2.9	4.5	107	86	71	83	49	23
21	300 mg	2.5	5.5	110	82	73	68	66	57
22	480 mg	2.2	4.9	84	63	69	56	66	64
23	480 mg	2.1	3.3	123	71	60	60	61	36
24	480 mg	4.2	7.4	87	68	65	48	57	58
25	480 mg	4.4	7.5	85	51	52	55	63	38
26	600 mg	3.2	4.4	86	68	86	86	44	27
27	600 mg	2.5	5.5	88	68	60	62	66	53
28	515 mg	2.4	4.8	92	67	71	67	68	54
29	515 mg	3.3	5.3	113	83	76	63	53	48
30	515 mg	2.8	4.9	84	72	73	59	50	54
31	515 mg	2.8	3.8	83	87	64	89	23	0
32	300 mg	2.6	3.9	78	70	54	52	41	36

Table 2.1 (cont'd)

Patient number	Dose	Cardiac output (L/min) before	Cardiac output (L/min) after	Mean systemic pressure (mmHg) before	Mean systemic pressure (mmHg) after	Mean pulmonary pressure (mmHg) before	Mean pulmonary pressure (mmHg) after	% fall in systemic resistance	% fall in pulmonary resistanc
FEDIPINE (sublingual)									
32	20 mg	2.23	5.16	73	76	63	58	55	60
ENTOLAMINE (i.v.)									
33	5 mg	6.7	8.0	100	98	45	35	18	33
	mean	3.42	5.28	94.3	84.8	64.1	6.18	40.8	37.8
	± SE	0.20	0.26	2.84	3.09	2.16	3.20	3.01	3.27
	P	< 0.0001		< 0.0001		NS		< 0.0001	< 0.0001

efers to cases where cardiac index was given instead of cardiac output. The values of these two cases, were excluded from the statistical analyses.

3. Objectives

The purpose of this cooperative study is to establish a patient registry to obtain and evaluate data on the natural history, etiology, pathogenesis and treatment of primary pulmonary hypertension. From this organized effort, fresh insights may be gained into its etiology and pathogenesis, new strategies may evolve for its early detection and rational therapeutic measures may be developed. The analysis of the results will provide guidelines for physicians dealing with these patients. Overall, lessons from the primary pulmonary hypertension case registry will prove meaningful for the management of more common types of pulmonary hypertension admitting definite etiologies.

Some specific aims have already been identified and are listed below:

1. Characterize the distribution at time of diagnosis of patients having primary pulmonary hypertension according to the following variables:

   a. Demographic variables such as age, sex, race, residence history, etc.

   b. Past medical history including dietary history and exposures to drugs as well as to other environmental exposures.

   c. Family history of pulmonary hypertension and associated disorders.

   d. Physical and laboratory findings at the baseline medical examination including symptoms.

   e. Hemodynamic findings at the baseline catheterization including responses to drug challenges.

   f. Pathological findings from the baseline lung biopsy.

2. Examine interrelationships among the variables specified above with special emphasis on determination of relationships between responses to drug challenges and the demographic, physical,

laboratory, pathological and hemodynamic variables measured at baseline.

3. Characterize the distribution of duration of survival from initial diagnosis and examine the effects on duration of survival of the following variables:

   a. Demographic variables, past medical history, dietary history, exposures to drugs, and other environmental exposures as measured at the baseline visit.

   b. Changes from the baseline visit in the physical, laboratory, hemodynamic and pathological variables.

   c. Medical interventions from time of initial diagnosis.

4. Characterize the distribution of changes from the baseline visit in physical, hemodynamic, laboratory and pathological variables and identify correlates of these changes.

5. Increase knowledge concerning the etiology of primary pulmonary hypertension.

4. Study Design

4.1 General Overview of the Study Design

A registry will be developed consisting of patients having primary pulmonary hypertension diagnosed or treated at 37 participating clinical centers. Although all patients currently being followed by the clinical centers would be eligible for entry into the registry, the study will focus on new cases.

A new case is defined as any case seen at a participating center for the first time during the study period (7/1/81 to 6/30/84) and diagnosed at the center as having primary pulmonary hypertension. This diagnosis would be on the basis of a right heart catheterization and possibly other diagnostic tests (e.g., lung biopsy). All other cases still being actively followed by the clinical investigator are eligible for inclusion in the registry as well. These cases are termed current cases. The DCC will request follow-up information on all patients in the registry at regular six-month intervals after the baseline examination. These requests will also focus on new cases.

Data from patients in the study group will be recorded on standardized forms at the participating clinical centers and sent to the Data and Coordinating Center at the University of Illinois. Here it will be entered on a computerized data base. The study pathologist, [redacted] will perform analysis on lung biopsy and necropsy material. The results of the pathological analyses will be forwarded to the University of Illinois and entered onto the data base.

Data management and statistical analyses will be performed at the Data and Coordinating Center. Findings will be discussed at quarterly meetings of the Steering Committee and at an Annual Meeting. This Meeting will include all principal investigators from the participating clinical centers as well as Steering Committee members and staff from the NHLBI program office and from the Data and Coordinating Center.

It should be emphasized that this is a registry rather than a clinical trial. The management of patients including drug therapies will be in conformance with the usual practice of the clinical centers. Although the Steering Committee may from time to time propose some procedures for patient management or diagnostic testing, the participating centers are free to accept or reject such proposals. Participation in the registry does, moreover, entail a committment on the part of the clinical centers to submit data on each patient entered in the registry to the Coordinating Center at regular intervals and to interact with the Coordinating Center on the maintenance of the data on these patients.

4.2 Definition of Primary Pulmonary Hypertension

As discussed earlier, primary pulmonary hypertension remains a diagnosis of exclusion. In order to make the diagnosis as accurately as possible, attempts should be made to exclude any secondary cause for the pulmonary hypertension. Since the possibility exists that a patient with primary pulmonary hypertension could also have some coexisting heart or lung disease, the physician should decide if the coexisting disease could, in and of itself,

account for the pulmonary hypertension. If not, that patient should be included as a patient with primary pulmonary hypertension. In addition, every patient should have pulmonary hypertension documented by hemodynamic measurement (defined as a pulmonary artery pressure greater than 25mm Hg at rest or greater than 30 mm Hg with exercise, and a resting pulmonary artery wedge pressure or left arterial pressure not greater than 12 mm Hg).

The following conditions should be excluded as a possible clinical cause of the pulmonary hypertension:

a. Pulmonary hypertension within the first year of life, and congenital abnormalities of the lungs, thorax (such as scoliosis) and diaphragm.

b. Congenital or acquired cardiac disease.

c. Demonstrable pulmonary embolic disease (by lung scan and/or pulmonary angiography).

d. Pulmonary airways disease

e. Interstitial lung disease.

f. Hypoxic pulmonary hypertension associated with impaired ventilation (either central or peripheral).

g. Collagen vascular disease causing significant pulmonary parenchymal, airways, or hypoxemic lung disease.

h. Parasitic disease (such as schistosomiasis or filariasis).

i. Peripheral pulmonary artery stenosis.

j. Pulmonary venous hypertension.

k. Multiple pulmonary artery thrombosis (secondary to sickle cell disease).

Several defined subsets of patients who have both pulmonary hypertension and an "associated" condition should be reported. These include:

a. Hepatic cirrhosis.

b. Collagen vascular disease (not felt to be significant enough to account for the pulmonary hypertension on the basis of pulmonary parenchymal diasease, pulmonary airways disease, or hypoxemic lung disease.)

c. Raynaud's disease.

d. Pulmonary hypertension possibly related to diet or drug ingestion.

Some patients will have an open lung biopsy as part of their initial evaluation of pulmonary hypertension. All patients who meet the clinical criteria for primary pulmonary hypertension should be entered and continously followed in the study, even if the pathologic findings on lung biopsy suggest an etiology other than those felt to be consistent with primary pulmonary hypertension.

4.3 Data Collection Instruments and Collection Procedures

There are three data forms that have been developed for this study. Form I is the baseline reporting form; Form II is the follow-up reporting form; Form III is the cause of death report form. Detailed instructions on the procedures to be used both in performing the examinations and testing, and in completing the forms are given in the Manual of Operations and Procedures (MOOP) which will be distributed to all the clinical centers. We urge all of the investigators at each clinical center who will be involved in this project to read this manual carefully before completing the reporting forms.

4.3.1 Baseline Evaluation

Enrollment of Patient into the Study Group

Both new and current cases of patients with PPH will be entered into the study. It must be stressed that data collection for new cases should take precedence over that of current cases. Similarly, the Data and Coordinating Center (DCC) staff will focus efforts on new over old, but in no sense should this be interpreted as a discouragement to investigators who wish to provide information on current cases.

A new case is defined as a patient who is, for the first time, seen by the investigator and entered into the study. The patient may have no previous known diagnosis of pulmonary hypertension from a referring physician. The initial reporting forms have sections covering the patient's history, physical exam, and laboratory data that should be filled out by the investigator based on data acquired by him. (in other words, all data regarding these patients will be prospective in nature). Data acquired by a referring physician previously may be submitted on a separate form and should be noted as such.

A current case is defined as a patient with known primary pulmonary hypertension whom the investigator has been following prior to the onset of the registry (July 1, 1981). All prospective data acquired on these patients should be reported on the follow-up forms. Data acquired by the investigator prior to the onset of the registry may be reported on a separate form, and should be noted as such.

The baseline reporting forms will have sections for the entry of data based on the history, physical exam, and laboratory data. Any investigator may routinely perform other tests not included on the data forms, or may choose not to perform certain tests provided for in the forms. The investigator should feel free to decide independently how to evaluate any given patient. The following suggested evaluation is based on what is believed by the Steering Committee to represent an accurate, thorough, and useful evaluation. It should be appreciated that without some uniformity of evaluation of these patients in the registry it will be extremely difficult to draw any conclusions about the similarity of or about differences between patients entered into the registry.

The following information is collected on the patient's baseline evaluation form:

1. Identifying data.
2. Present medical history.
3. Past medical history.
4. Family history:
   Results of screening of the immediate family for possible pulmonary hypertension.
5. Physical examination.

6. Laboratory testing:
   Includes chest x-ray, electrocardiogram, CBC, prothrombin time and sedimentation rate, full respiratory function tests, ANA titer, pulmonary ventilation/perfusion scanning, treadmill exercise testing, M-mode and 2-D echocardiograms, and open lung biopsy. Patients with suspected hepatic cirrhosis should have the appropriate documentation included in the section provided, as should patients with associated collagen vascular disease and possible diet or drug related pulmonary hypertension.

7. Etiology:
   Includes information on defined subsets.

8. Hemodynamic data obtained from right heart catheterization:
   Include any information obtained with exercise testing and drug intervention.

4.3.2 Follow-up of Patients in Study Group

It is suggested that follow-up visits between the patients and investigator be scheduled at least at six month intervals, so that meaningful data may be accrued about the course of the illness in these patients. The DCC will provide reminders that a six month follow-up should occur (only if no other information has been provided during the time since baseline or last follow-up).

The investigator may choose to see patients at an earlier date, or may be unable to follow-up some patients because they live too far away. All information gathered at the follow-up visits should be recorded in the appropriate section of the follow-up forms. Each individual investigator is free to choose the manner in which patients should be evaluated or followed, but it should be kept in mind that only by obtaining serial tests in these patients, even if the patients are unchanged in their clinical course, will it

be possible to draw conclusions abut the value of any type of testing in patients with primary pulmonary hypertension. Data obtained on patients entered into the registry from sources other than the clinical centers can be submitted, but should be done so on a separate form and indicated as such. The following evaluation has been suggested by the Steering Committee as appropriate for the follow-up of these patients:

1. History since the previous visit.
2. Physical examination.
3. Laboratory testing:
   Includes chest x-ray, electrocardiogram, CBC, respiratory function tests with arterial blood gases, pulmonary ventilation/perfusion scan, treadmill exercise testing, M-mode and 2-D echocardiograms.
4. Hemodynamic data obtained from right heart catheterization:
   Include information obtained with exercise and drug intervention.
5. Family history.

4.3.3 Death Information

Information on causes of death as well as any clinical information available before death will be obtained for each patient in the study group who dies during the course of the study. Refer to the discussion of follow-up data collection above.

4.3.4 Recommended Time Schedule for Data Submission

In order to maintain the integrity of the data base with respect to proper classification of baseline and follow-up data and to minimize the efforts of

investigators in data collection and transmission, we propose the following guidelines. The baseline data collection period will be considered as terminating two (2) weeks from the date of the catheterization on which the diagnosis is based. It is left to the discretion of the investigators as to which diagnostic and therapeutic procedures will be performed during that period. Although this guideline is not meant to be inflexible in the face of extenuating circumstances which are bound to arise, it is hoped that it will be followed in most cases, since a narrow collection period will reduce variability arising from lack of uniformity in collection periods.

The follow-up data collection period begins two weeks from the date of diagnosis and terminates six (6) months from that same date. The investigators are encouraged to collect and submit data at least every six months, and more if they so desire. The intention here is that the investigator may be able to perform as many tests as is desired during the patient's follow-up visits. This system allows investigators the flexibility to schedule tests at their convenience and at the convenience of their patients over a longer period of time. It was felt by the Steering Committee that this flexibility is important and outweighs the problems associated with not having all procedures performed at a fixed point in time.

5. Pathology Specimens, Examination and Data Recording

A system for analysis of pathology specimens (including lung biopsy, stored plasma, and other tissue which may have subsequent usefulness) taken from patients entered into the Registry will be established as part of this study.

Pathology specimens submitted by the clinical centers will be received by the Registry Pathologist for complete evaluation. This evaluation procedure includes two major components. One is study by light miscroscopy and provision of detailed, written, systematic description with citing of critical findings by "Key Word" system. The detailed written description will be made one component of the Registry permanent data, with storage as hard copy.

Further analysis of pulmonary pathology specimens will be accomplished to define quantitative characteristics of vessels (see Methods, Section 5.1 below). This organized information will be stored with the patient data record as hard copy, and as a component of computer stored patient data. Objectives of pathological analysis are as follows:

a. Determine the nature of anatomic changes in pulmonary blood vessels of patients with primary pulmonary hypertension.

b. Assess the severity of lesions quantitatively in order to evaluate possible relationships between structural alterations and hemodynamic measurements.

c. Determine the usefulness of the current grading system of vascular changes.

d. Evaluate the predictive value of lung biopsy in relation to diagnosis and response to therapy.

Although highly desirable the following studies are beyond the scope of the registry and may be undertaken by direct collaboration between participating investigators.

a. Analysis of cell population in lungs of patients with primary pulmonary hypertension.

b. Ultrastructural studies on vascular wall components.

c. Correlation with wedge angiograms.

d. Correlation with lung scans and vascular pathology at biopsy or autopsy.

5.1 Methods

An essential prerequisite to accurate evaluation of histopathology slides is the standardization of the protocol for sampling and processing lung specimens for the preparation of faultless histologic slides.

5.1.1 Qualitative analysis of histopathology slides

Sections stained with hematoxylin eosin (H&E), Van Gieson-Weigert for elastic tissue, and Mallory trichrome must be available in each case. It is preferred that unstained slides be sent to the Registry Pathologist since staining techniques vary in different hospitals. For biopsies at least 3 paraffin blocks must be cut; autopsy material must include at least 3 blocks per lung lobe (i.e., 15 blocks). Elastic arteries are usually not included in biopsy material; thus the qualitative analysis is limited to muscular pulmonary arteries, arterioles, veins, alveolar septa, extraalveolar interstitial space, airways and bronchial vessels. Muscular pulmonary

arteries are readily identified in slides stained for elastic tissue by the presence of internal and external elastic laminae. Arterioles are vessels less than 100 um in external diameter with a single elastic lamina. They usually can be distinguished from venules by the accompanying airways. But in biopsies this is not always feasible.

The protocol for qualitative analysis and grading of lesions in histopathologic slides is shown in Figure 5.1.

5.1.2 Quantitative analysis

In biopsies, all arteries and 50 arterioles per slide will be measured. For autopsy material, at least 50 muscular arteries and 50 arterioles are measured. Only vessels in transverse sections are measured. Slides stained with elastic Van Gieson will be projected onto a graphic tablet by a camera lucida attached to a light microscope. The tablet is equipped with a stylus connected to an Apple computer. The magnification is entered and the outlines of the various components of the vessel wall traced with the stylus. For arteries, the measurements include areas of lumen, intima, media and if needed, adventitia. For arterioles the area of lumen and total wall is measured. Calculated is the alveolar/vessel ratio, total and mean cross sectional areas of vasculature, relative contribution of vascular wall component to its mean area, and lumen/wall ratios for vessels of different size.

FIGURE 5.1

QUANTITATIVE ANALYSIS OF PULMONARY SPECIMENS

AND GRADING OF VASCULAR CHANGES

Registry # Date

	Percent wall thickens				
	<10	10-25	25-75	>75	Combined
	G1	G2	G3	64	score
Arterioles	n_1/n	n_2/n	n_3/n	n_4/n	$\frac{(1xn_1)\&(2xn_2)\&(3xn_3)\&(4xn_4)}{S\ n}$
Arteries	n_1/n	n_2/n	n_3/n	n_4/n	$\frac{(1xn_1)\&(2xn_2)\&(3xn_3)\&(4xn_4)}{S\ n}$

Qualitative Evaluation

Arteries

Media hypertrophy	mild	moderate	severe
Concentric Intimal Prolif.	mild	moderate	severe
Excentric Intimal Prolif.	mild	moderate	severe
Recanalized/Org. Thromboemb.	#/S n		
Recent Thromboemb.	#/S n		
Angiitis	#/S n		
Plexiform	#/S n		
Dilatation	#/S n		
Siderosis	#/S n		
Other	#/S n		

Arterioles

Muscle Extension	mild	moderate	severe

Veins

Intimal Fibrosis

Thrombi

Parenchyma Airways

Inflammation	mild	moderate	severe
Fibrosis	mild	moderate	severe
Other			

5.2 Protocol for Lung Biopsy Examinations

Lung biopsy is an optional test associated with a certain risk for the patient. To obtain the most information from this procedure, investigators are urged to follow this protocol.

1) Selection of type of biopsy:
   Wedge (open) biopsies provide enough small arteries and artioles for qualitative and quantitative analysis. Transbronchial biopsies are not suitable for the proposed study of primary pulmonary hypertension.

2) Site of biopsy:
   The lingula and the tip of the right middle lobe should be avioded since they often reveal thickening of vessels and interstitial fibrosis in otherwise healthy lungs. The sampling of either lower or upper lobes does not seem to be of critical importance. However, if feasible, biopsy site should be the same for all cases.

3) Fixation and sectioning:
   The lung is inflated by the anesthesiologist, clamped between two clamps and removed by the surgeon. The specimen is immersed in the inflated state into 10% buffered formaldehyde or Bouin's fixative. The properly identified specimen is then transorted to the pathology laboratory.

A small sample may be cut for immunofluuuorescence and ultrastructural studies (see below). The specimen removed for light microscopy should be of adequate size, usually 0.5 x 2 x 3 cm. The fixed lung slices are further fixed under vacuum (-10 mm Hg) for 4-6 hours, dehydrated and embedded in paraplast. Sections are cut at 4 um thickness. Unstained sections from at least 3 different blocks are sent to the Registry. They will be stained with hematoxylin and eosin (H&E), Van Gieson-Weigert for elastic tissue and Mallory's trichrome for connective tissue. It is anticipated that each biopsy will generate between 3-6 blocks.

The site of biopsy should be recorded by the surgical pathologist. Name, age, sex and other pertinent data will be affixed. These data and the sections are mailed in a slide carton to the Registry Pathologist.

Although immunofluorescence and ultrastructural studies are not comtemplated by the Registry, it is recommended that the contributing hospital will save material from these rare patients for such studies.

5.3 Autopsy

Efforts should be made to obtain autopsies on patients in the Registry. The autopsy permission could be limited to chest incision. This approach is preferable to permission for "heart and lung only" since permission for chest incision allows inspection and sampling of abdominal organs. If the patient is recently expired and the autopsy is performed in a hospital, the lungs should be fixed by intratracheal perfusion with 10% formalin at 20 cm. of water. If possible, post-mortem angiograms should be performed. For this purpose, before fixation, the pulmonary vasculature is perfused with a mixture of Barium-gelatin or Renografin-gelatin at the systolic pulmonary pressure of the patient in life. Careful examination of the heart and venous system should be done. A copy of the autopsy protocol, longitudinal section of both lungs or samples of lungs from every lung lobe should be sent to the Registry. The site of sampling should be marked on the pathology transmittal form.

5.3.1 Autopsy of patients dying at home

Often patients die at home and several days may pass before the

clinical investigator is notified of such death. Alternatively, the patient may die suddenly and an autopsy may be performed by the Medical Examiner. In these instances efforts should be made to obtain heart and lung from the embalmed body or from the Medical Examiner. The tissue should be fixed in 10% formalin and shipped in plastic containers to the Registry for study. Although quantitative analysis may not be possible, the material may provide useful information on modality of death and nature of lesions.

6. Data Management and Statistical Analysis

6.1 Collection, Storage, and Retrieval of Data

Collection of data for baseline, follow-up, and cause of death will be done at the clinical centers. The process of data collection will be done according to procedures specified in the Manual of Operations and Procedures (MOOP). The forms for collection provided by the DCC office are computer generated and self-duplicating, a feature which permits both the institution and the DCC to retain a copy. This is a great advantage if it becomes necessary to discuss any problems in the data submitted.

As soon as the clinician is able to confirm through cardiac catheterization that a patient has primary pulmonary hypertension, several routine data collection procedures will be followed. First, a unique patient ID will be generated by the clinician according to procedures in the MOOP. Second, the baseline reporting form (Form I) will be completed, and the original copy of this form mailed to the Data and Coordinating Center. (The clinician will keep the duplicate copy of the self-duplicating form.)

6.1.1 Receipt of Data by DCC

At the DCC, the project coordinator will log the date of form completion (and date received), patient ID and form-type as forms are received. The coordinator will then verify this information with the clinic, and complete an on-line computer registration form. The on-line procedure will either create a new patient record in the registry data-base or update a pre-existing

record. This verification is essential as all subsequent references to the patient's data will be in terms of identification information. Furthermore, by following this on-line procedure a search for duplicate ID's is automatically performed.

The project coordinator with consultation from the principal medical investigator (Dr. Rich) will visually examine all forms for accuracy. Any problems identified at this time will be resolved by telephone between coordinating center personnel and the clinic. It is felt that this interaction between coordinating center personnel and the clinics, at an early stage of the data collection process, will serve to resolve most problems in reporting, or misunderstandings of procedure which may occur.

Following the visual edit and error resolution, all data forms will be retained for examination and interpretation by the Coordinating Center's physician. The forms will then be assembled for coding and data reduction.

It is planned to code all open-ended data items. Such a reduction step accomplishes several goals of a multi-clinic registry. Primarily, coding of open-ended questions establishes an objective, non-ambiguous meaning for a given item. Secondary benefits are the reduction in size of the data records and the additional detailed examination of the data form. Uncommon responses are obvious and can point to the need for corrective actions. Existing coding schemes will be used where appropriate; new coding schemes will be developed where necessary.

6.1.2 Manual Data Entry

Subsequent to coding, the data forms will be entered onto a computer file using a cathode ray tube (CRT) terminal attached to an interactive computer program running in the IBM Series I minicomputer located at the School of Public Health. Some details of the operation of this program are pertinent to this protocol.

As the DCC develops forms, the programmer will generate a computer version of it called the form-image. For each form-type there will be a corresponding form-image. During a typical data entry session, the data clerk will simply command the computer to display the image on the CRT. The nature of the image is such that the clerk will transcribe the information from the form to the same or similar location on the image.

Automatic checks are included in the program regarding valid variable ranges and intra-form consistency. Values which do not conform to these specifications generate an error indication, and must be re-entered. If a third attempt is made to enter invalid data (as would occur, for example, if the value written on the form were truly out of range) an error record is created and a message is generated on the transaction report. These error records will be corrected following a resolution of the problem by the project coordinator, as in the error resolution procedure specified for the visual edit. The corrected records will be saved for inclusion in the next session batch. If corrections are delayed for some reason and cannot easily be made, a value indicating such will replace the erroneous item. Forms which have

been entered into the mini-computer will be stored until corrected or will be batched for submission to the mainframe IBM 370 computer located at the Chicago Circle campus of the University of Illinois (aproximately 1 mile from the School of Public Health).

A further capability of the point-of-entry edit is to examine a copy of case summary information from the registry data-base maintained on line at the local mini-computer. Verifying newly entered against case summary information will help to ensure that update transactions reaching the data-base are consistent with information already on hand. The primary output from this initial entry and edit is a print-out of transactions performed during the data entry session. The error file generated from data entry transactions is retained for backup purposes.

6.1.3 Automatic Data Management

The transactions resulting from a data entry session will be transmitted from the School of Public Health minicomputer to the host mainframe computer over a 4800 baud binary synchronous communications dial-up phone line. At the host site, a batch update (i.e., noninteractive) is performed. The expectation of a relatively small number of cases in the registry allows the data records to be disk resident. An update report is automatically produced as a result of the transaction. The updated version of the database is backed up to magnetic tape. The database system will then permit transmission of an updated summary file to the minicomputer. Each new data entry session follows this same process. Thus the most current summary information is maintained on site.

The update report will be reviewed and appropriate corrections will be made following resolution of any errors which are detected. We anticipate that most errors encountered at this stage will be mainly of a procedural nature, due to the editing performed at the time of forms entry.

At this time a batch edit will be run which checks characteristics of the full registry for validity and consistency. An edit report will be produced describing the contents of the entire registry data-base, as well as identifying fields in error. This report will be used to locate and correct items, as necessary.

Most reports will be created using the record selection and report generation capabilities of the Scientific Information Retrieval (SIR) data-base management system (DBMS). Some special purpose reports may require the creation of a sequential version of the data-base; this will easily be accomplished through data-base command language. The periodic report and summaries for the principal investigators, the clinics, and for NHLBI will almost certainly be generated through the data-base management system.

Analysis will be performed using standard statistical packages at the host computer site. The SIR data-base management system can create an SPSS system file (Statistical Package for the Social Sciences) using a simple specification in the control language. This system file may be used either directly as input to an SPSS analysis program, or converted to a SAS file for processing by SAS. The latter procedure has been used advantageously by the Coordinating Center for the Cooperative Study of Sickle Cell Disease, which

has developed and is maintaining a registry similar in nature but much larger than the one described in this document. Any analysis which cannot be performed using one of the packages will be coded in either PL/1 or FORTRAN, using a sequential version of the registry data-base. An extensive set of subroutine libraries at the host computer facility will aid in the accurate and timely completion of such applications.

In addition to backup procedures used at the minicomputer laboratory, the UICC Computer Center provides full backup of data. Security of the registry will be maintained by use of passwords, and security of all materials in the Data and Coordinating Center will be maintained by keeping locked all filing cabinets and office doors.

A diagram of the data collection and editing procedures is shown in Figure 6.1 for the manual collection and edits and in Figure 6.2 for the computer edits, storage and reports.

FIGURE 6.1 MANUAL COLLECTION AND EDITS

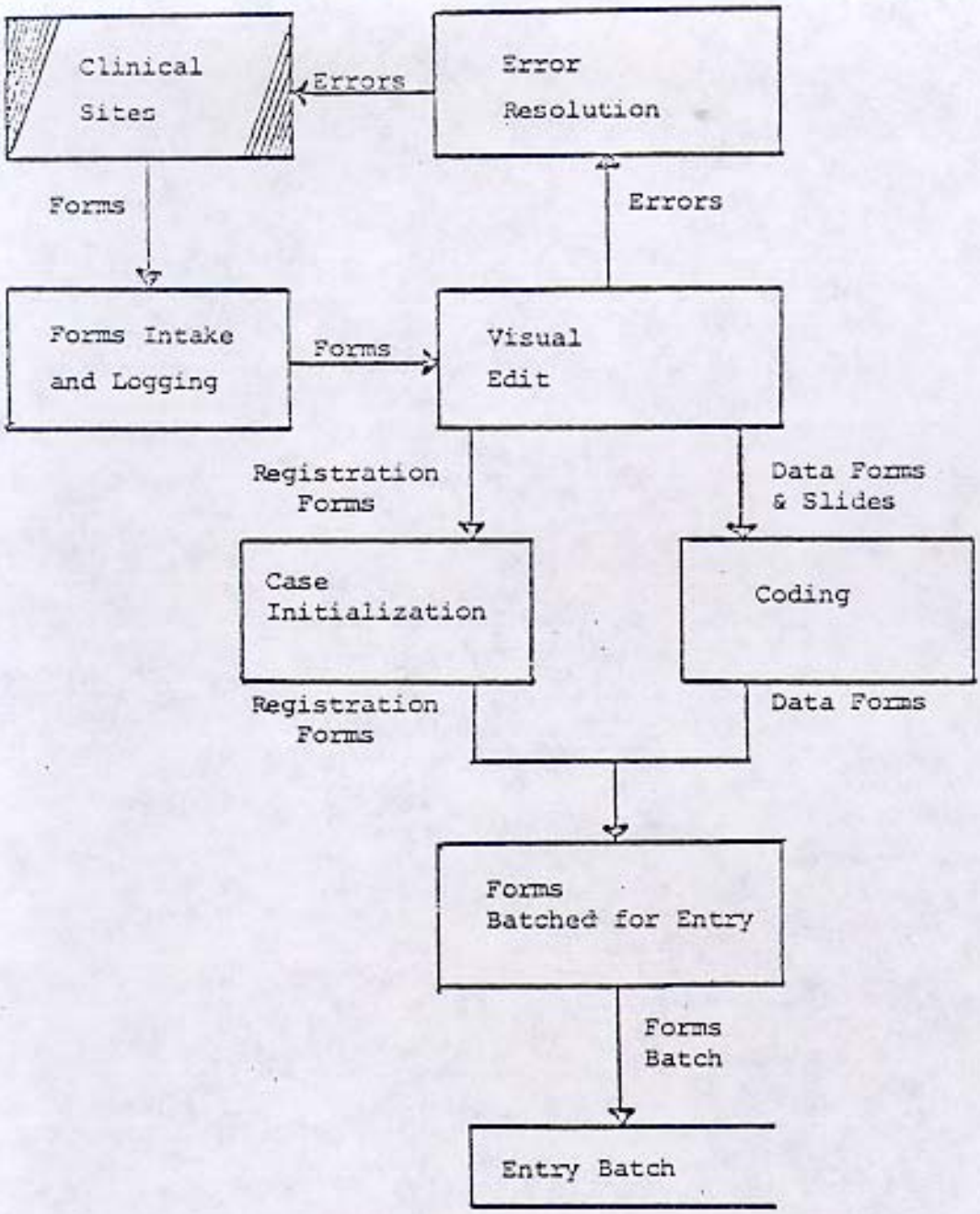
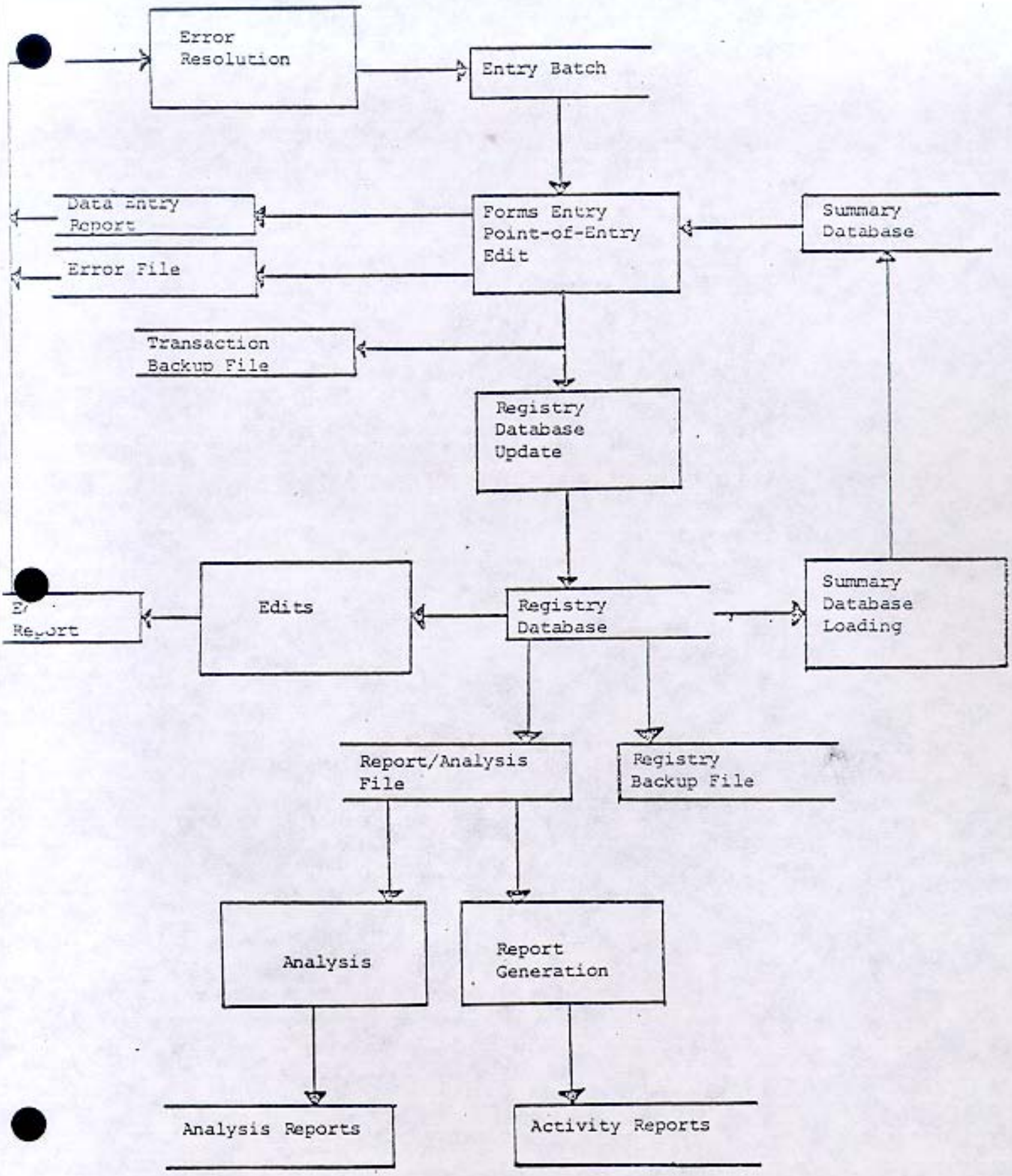


FIGURE 6.2 AUTOMATED EDITING AND PROCESSING



6.2 Quality Control of Data

6.2.1 Point of Entry and Automatic Data Editing

Sequence numbers will be assigned to all forms which are used by the registry. These numbers will be referenced whenever documents are transmitted between the clinics and the Coordinating Center, and will help to identify documents when the need arises. When forms are mailed in a batch to the Coordinating Center, a list of the forms included in the batch will be forwarded under separate cover. Form numbers and patient identifiers will be logged on the registry on receipt of the document. This procedure should prevent lost or duplicate forms. Forms will be produced on two part no-carbon paper in order that the clinics can retain a copy for their files. These copies can be referenced should any questions develop.

A visual edit of the forms upon their receipt at the Coordinating Center will serve to resolve problems of legibility, completeness or obvious inaccuracy at an early stage. Such errors, when detected prior to data entry, will not be propagated through the registry data-base.

The coding of open ended questions at the registry will standardize the responses to this type of item. A small sample of forms will be coded a second time and compared to the results of the initial coding. This will permit an assessment of the reliability of the coding and also help to identify ambiguous or unclear items.

Forms will be entered using a CRT under control of an interactive editing program. A replica of the form will be displayed on the screen, and data from the forms will be typed in the corresonding positions on the screen. This procedure minimizes errors in entry and item omission. An online copy of case summary information obtained from the registry data-base will be interrogated as each form is entered, permitting checks of newly entered data against archival information. In addition, the entry program provides checks as to valid data type, proper range, and intra-form consistency. (The use of such a method in the sickle cell project has proven to reduce the number of errors in transcription and to identify inaccurate recording of the forms).

This method is especially effective in detecting such errors as the existence of a duplicate form, missing forms, and forms out of sequence. Detection of fatal errors at the point of entry greatly enhances the error correction process and ultimately the integrity of the data-base. A modification of this system will permit certain data to be punched twice, providing a check on the error rate in punching. (This is described below under the rubric of data verification). During the form-to-CRT transcription, the computer will create edit-failure records or 'flags'. When transcription is complete a list these errors will be printed. Data forms which are error free are then grouped into batches and transmitted to the host computer. Records with errors are stored locally until the errors are resolved.

The project coordinator will resolve these errors after the problem is brought to the personal attention of the clinical investigators. Failed forms

will either be: eliminated from the invalid transaction file (they were duplicates); corrected, thus becoming valid transactions; conditionally corrected by overriding the edit program. (Conditional correction implies a situation where correction of a group of values or variables in the data base is necessitated).

An important function served by the transcription error report is to provide information on the frequency with which various errors are encountered. This is at least one point at which it may become possible to discern problems in data collection procedures. Obviously, errors in punching would be picked up at this point as well.

The set of records in the valid transaction file are then transmitted to a temporary disk file, and then automatically processed into the data base by SIR. Once in the data base the records go through more extensive quality control steps. For example, inter-form checks on variable consistency may be made. The error resolution procedures will be completely analogous to those at point of entry and will not be discussed further. The ultimate objective in DBMS is to ensure that errors in the data due to data handling procedures are prevented or quickly rectified so that in the final analysis either the item is the true value of the measurement or it deviates slightly from the true value because of slight random measurement errors.

The use of a Data Base Management System (DBMS) to maintain the computerized registry will have a very postive effect on data quality control. Use of a DBMS obviates the extensive reprogramming which is often necessary

when changes are made to the file stucture. Revisions of forms are simplified as all references to items on the data-base are by the name of the item rather than its position on the file. The implementation of new forms is also facilitated through the record linkage capabilities of the DBMS. A new form type may be associated with the patient records by a relatively simple restructuring of the data-base by which the new record type is linked to existing information.

A major benefit of a DBMS lies in the flexibility it provides for editing, report creation and analysis. Editing and record selection become a simple matter of combining a small set of special purpose, high level instructions. The schema definition which describes the structural relationships among items in the data-base is a feature unique to the SIR DBMS. This schema permits a final check on items as they are added to the data-base. The characteristics of each field may be described in this schema; invalid values which in some manner have failed all previous error detection schemes will almost certainly be identified at this stage. The non-volatile nature of the schema which defines the data-base as a whole, ensures that a consistent set of checks will have been performed on the database, even though the definitions may have evolved through several modifications.

6.2.2 Data Verification-the key data verification window

A major function of the DCC is to ensure that the data items on the data forms are entered into the data base exactly as they appear on the forms. By comparison, the procedure of keypunch-verification used so often in the past

maintains data quality but delays the rate of entry into the system. The growing confidence in the relatively new CRT point of entry methods derives from two advantages, namely a reduced error rate during 'punching' and a reduced turn-around time for entry into the data base. Neither keypunch verification nor CRT point of entry can detect errors in data recording, a problem which is apprehended using variable range checks, as well as inter- and intra- form checks.

The DCC proposes to supplement the CRT point of entry procedure by establishing a "verification window". This is done by identification of a set of "key" variables which will be entered twice. The particular variables included in this set will be identified by the Steering Committee. It is anticipated that this set would include demographic and other "identifying data", hemodynamic data and other items considered to be crucial. This verification window is adjustable, since additional variables can be easily added to the set. Visual cues such as the placing in boxes of items on the data form that are to be entered twice can be used to assist the data entry clerks.

This verification window concept was developed after identifying the component tasks of data entry and attempting to judge the relative time needed to perform each one. These tasks can be enumerated as follows:

(1) Proper recording of data and concomitant visual editing,

(2) Efficient form to CRT transcription,

(3) Generating and implementing point-of-entry edits,

(4) Error processing in the DBMS,

(5) Subsequent quality control checks prior to publication.

In the design of a data entry system, valuable time resources as well as funds are allocated to the tasks of keypunching, manual editing, and on-line computer editing. A system in which all data items are double entered allocates considerable time resources to the task of keypunching and can often cause delays in the preparation of periodic reports on the status of the data base. Such delays are especially problematic in cooperative studies such as this in which important decisions are made at quarterly meetings of a steering committee. The verification window system proposed here avoids the time dependence of the entire system on a single step - namely keypunching while allowing the flexibility of double entry of additional variables at a later time.

Several criteria for justifying the selection of a subset of variables may be applied. First, variables (such as hemodynamic data) necessary to verifying the diagnosis should be punched. Secondly, numeric data with a small level of variation (for instance a small coefficient of variation) would be punched twice. In complementary fashion, variables with high variability, or those not crucial to the diagnosis, or ancillary to general medical understanding of the disease would receive lower data coding priorities. For certain lower priority items, additional time would thus be available for resolving coding problems. The fact that the window or variable subset can be changed gaurantees that the integrity of the database system is preserved.

Finally, it is expected that prior to release of publications or compilation of final results additional review of the pertinent data items is typically implemented.

Periodically, a sample of cases on the data-base will be listed and this listing compared to its originating documents. This assessment will offer a gauge of accuracy and reliability of the registry and also will point out the need for modificaton of collection and entry procedures should the error rate prove to be unsatisfactory. Comparisons at the clinic between the monthly activity report and the original files will serve a similar assessment function, as would cross checking of logically related variables within or among the data forms.

6.2.3 Data Security

The security of the system with regard to inadvertent deletion or modification merits additional comment. Data entry occurs through the minicomputer; these interactions and subsequent transactions with the SIR data-base generate error reports. At the SIR level up to 30 levels of security restrictions are possible. This includes specifying read, write and edit access for particular individuals. For PPH, only the coordinator and the P.I. will have edit access to the SIR data-base. Backup of all files will be done by PPH programmers on a regular basis using magnetic tapes. The UICC system independently will back-up files every 2-3 days. Finally, a well-developed system of security passwords is built into the system restricting unauthorized access to program data sets and magnetic tapes.

6.3 Statistical Analysis

The overall goals of this cooperative study are to gain new insights into the natural history, etiology and pathogenesis of primary pulmonary hypertension and to assess the effectiveness of therapeutic measures currently used to treat this disease. To accomplish these goals, the study design is that of an observational study which would follow patients from the point of diagnosis to the end of the study or to death (whichever comes first). Data collected on each patient at baseline (time of first catheterization) and at subsequent visits can be grouped into the following categories:

Baseline Data

1. Demographic Information (e.g., sex, race, residence history, etc.)
2. Medical History (congenital heart disease, family history of pulmonary hypertension and other associated disorders, current and past medications, pregnancy history, dietary history, etc.)
3. Findings at Baseline Medical Examination (height, weight, chest x-ray findings, EKG findings, hematology, spirometry, arterial blood gases, biochemistry, etc.)
4. Non-invasive Testing Conducted at Baseline (radionuclide studies, treadmill, etc.)
5. Baseline Control Hemodynamic Data (cardiac output, pulmonary arterial pressure, pulmonary capillary wedge pressure, systemic arterial pressure, pulmonary vascular resistance, systemic vascular resistance, etc.)
6. Hemodynamic Data Following Drug Challenges (name of drug, class of drug, dosage, response at various times after injection of drug with respect to cardiac output, pulmonary and sytemic arterial pressures, etc.)
7. Pathological Findings From Lung Biopsy (medical hypertrophy, intimal fibrosis, etc.)

Follow-up Data

1. Time Since Baseline Examination (6 months, 1 year, etc.)
2. Survival Status (Alive/Dead)
3. Findings at Follow-up Examination (height, weight, symptomatology, laboratory findings, etc.)
4. Medication History Since Baseline Examination
5. Hemodynamic Findings at Follow-up Examination
6. Pathological Findings at Follow-up Examination

Cause of Death Data

1. Cause of Death (Including immediate and secondary causes).

Patients will be recruited into the study from the thirty-five clinical centers on an ongoing basis during the three year course of the study so that there will be variability among the subjects with respect to length of time followed. In addition, although a certain amount of standardization of procedures will be expected of clinical centers, there will be some variablity among these centers with respect to patient management and to the type of diagnostic tests performed. These issues will have considerable impact on the types of statistical analysis that can be performed and on the questions that are likely to be addressed in the analysis plan. Statistical power will be a crucial issue since the number of patients recruited will be relatively small (400-600 patients).

6.3.1 Interim Data Analyses

One of the first products of the DCC will be exploratory statistical analyses of data acquired before the registry termination. This will

generally be limited to descriptive analyses of the baseline findings. Follow-up and cause of death data is expected to accrue more slowly, but will be presented where pertinent or when requested.

This interim analysis will furnish information concerning characteristics of patients with primary pulmonary hypertension at the time of first catheterization and will entail cross-tabulations of patients by age, sex, race, and other demographic variables. In addition, the distributions of survival time, selected hemodynamic variables and selected pathological variables will be examined for the entire group of patients in the registry as well as for various demographic subgroups.

Further analysis of the baseline findings would attempt to characterize the response to the drug challenges administered during the right heart catheterization at the baseline examination. Dependent variables in this analysis would be changes in cardiac output, pulmonary and systemic vascular resistances, etc.

These descriptive analyses will entail use of relatively straightforward techniques such as simple frequency distributions and crosstabulations; descriptive statistics for quantitative variables; t-tests, chi squared tests and possible ANOVA. It is anticipated that the appropriate contingency table and summary statistics programs in SAS or SPSS would be used in this phase of the analysis.

It should be noted that, at best, these interim analyses would indicate trends or would identify emerging patterns. They might be useful in targeting areas where data quality is poor and needs improvement, and in indicating areas where more intensive research should be directed.

6.3.2 Final Analysis of Registry Data

At the termination of the study it is expected that very detailed statistical analyses of the data will be undertaken. Because of the low rate of accrual, and the lack of statistical power, use of complicated procedures will tend to be ineffective until all the data is accrued. Prior to this final analysis, preliminary results obtained on partial data may reflect biases arising from such artifacts as different rates of data submission among investigators. In contrast, after termination, the complete examination of follow-up and cause of death data will be most fruitful and informative since a larger quantity will have accrued and all delinquent forms will have been submitted. Also, a final concerted check on the status of patients who were alive at last follow-up will have been made regarding, at the least, survival status as of the termination date of the study.

At this stage of analysis it is important to note the existence of statistical problems guaranteed to arise. First, because of the relatively small number of patients expected to accrue, statistical power may not be as high as ideally hoped. Second, owing to data collection patterns certain weak statistical patterns observed in earlier analyses of the the data could finally emerge or disappear. This should not inhibit investigators in their

interpretations of the data derived from sound biological models. Third, there will be a limit on the detail which can be expected from the ultimate statistical analyses. Thus it is statistically meaningless to analyze data on individual patients, but it is statistically desirable to find homogeneous groupings of patients that are as large as possible. The most useful type of advanced statistical procedures permit analyses that account for the action of several variables at a time.

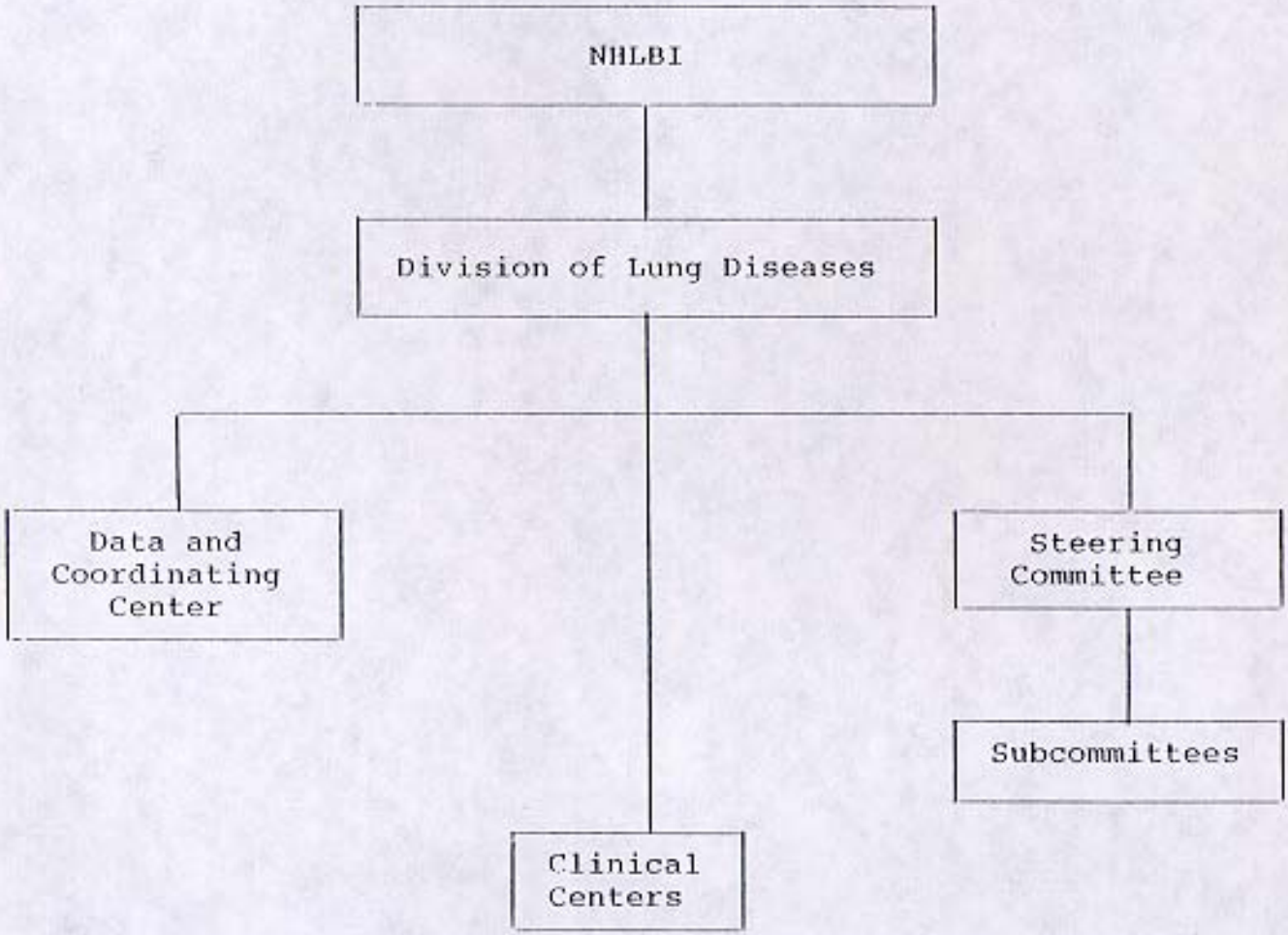
The multiple linear regression programs in the SAS library can be used for such examination of quantitative dependent variables. The multiple logistic regression program in the SAS Supplemental Library can be used for examination of dichotomous dependent variables. We have used these programs extensively in our research projects. As an example of a typical analysis, one might use lowering of pulmonary arterial pressure as a dichotomous dependent variable with type and class of drug, age, sex, race, presence of pathological abnormalities, arterial blood gas levels, and other findings as independent variables in a logistic regression model. This type of analysis would identify those factors that are associated with favorable responses to a particular medication and would be useful in identifying subgroups of patients likely to be responsive to particular medications.

A third phase of the analysis would involve examination of the longitudinal data. In this phase, we would examine survival status, hemodynamic variables at follow-up, functional status and symptoms, physical examination findings and hemodynamic findings in relation to medications taken

during the interval from baseline to follow-up. It is anticipated that actuarial methods and Cox regression techniques would be suitable for this phase of the analysis. In this phase of the analysis, we would also examine the occurrence of adverse reactions to the medications using Cox regression techniques.

FIGURE 7.2

ORGANIZATIONAL STRUCTURE OF PATIENT REGISTRY FOR THE CHARACTERIZATION OF PRIMARY PULMONARY HYPERTENSION



8. Time Phased Schedule

A list of the major tasks and activities for this project along with a tentative time table for their completion is shown in Figure 8.1. This preliminary schedule would be subject to periodic evaluation and would be modified to accomodate any changes in the study protocol. As part of our management plan, we PERT out major activities and deliverables in full detail.

FIGURE 8.1 TIME PHASED SCHEDULE

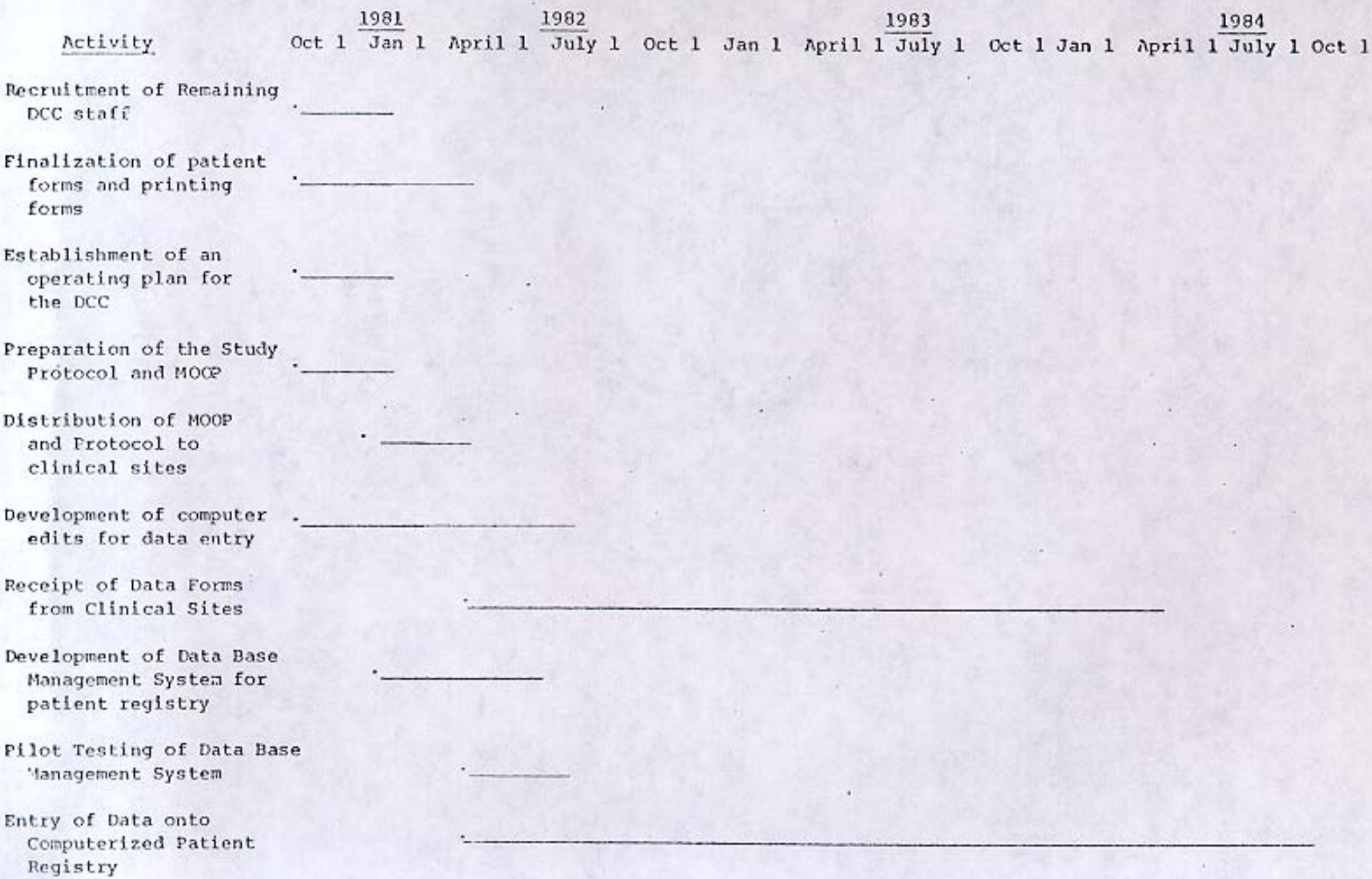
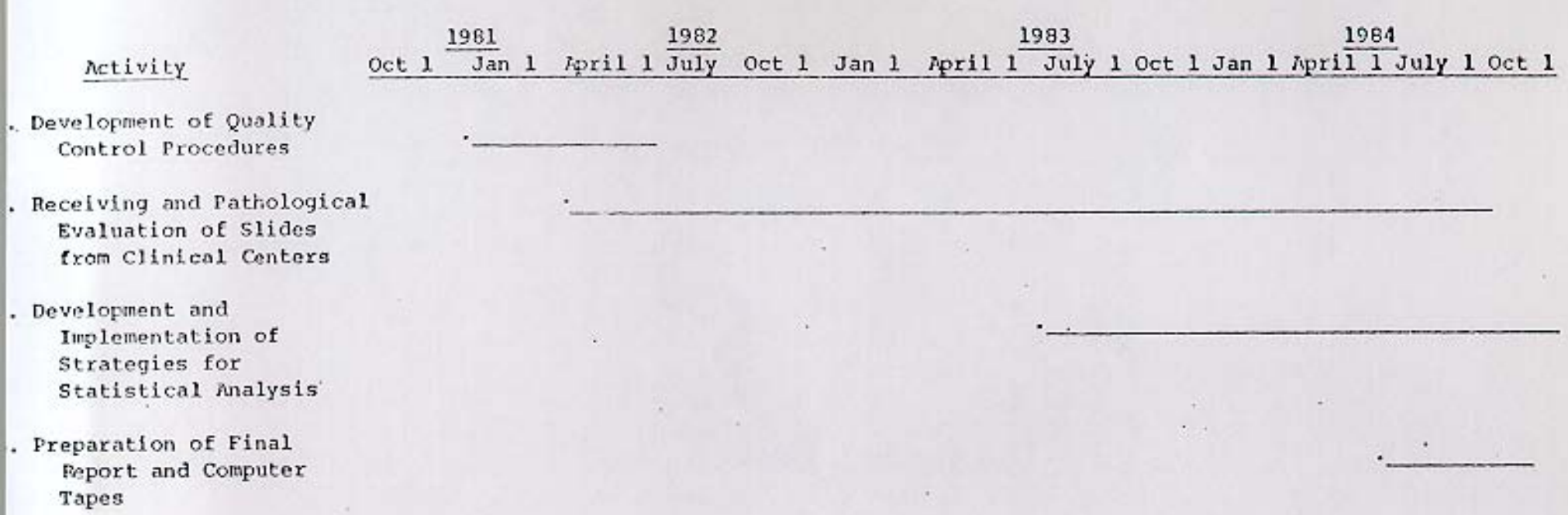


Figure 8.1 Continued



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