NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

DIVISION OF LUNG DISEASES

PROTOCOL

FOR

INTERMITTENT POSITIVE PRESSURE BREATHING (IPPB)

COLLABORATIVE PROGRAM

11/30/80

CONTENTS

INTERMITTENT POSITIVE PRESSURE BREATHING IN THE LONG TERM MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

1. INTRODUCTION

The importance of chronic obstructive pulmonary diseases (COPD) as a national health problem, is considerable at present and appears to be increasing rapidly. Available data indicate the prevalence of all chronic respiratory conditions to be approximately 20 percent of the United States population and 40 percent of all persons having any chronic disorder (1). Some 2.5 million persons have limitations of activity because of chronic lung disease (1). The absolute mortality for COPD in 1975 was 19/100,000 (2). Mortality rates, however, fail to describe in full the adverse effects of these diseases because death is usually preceded by a prolonged period of disability and suffering. In addition, prolonged and repeated hospitalizations are often economically and emotionally devastating for the patients and their families, while at the same time being a major economic loss to the community and a drain on community medical resources.

The total economic impact of these diseases can be estimated in terms of the direct costs of treating patients, reduced productivity due to morbidity and reduced productivity due to mortality. In 1972, direct costs of hospital treatment, physician services and prescribed drugs were estimated to be $803 million. In the same year, costs in terms of lost earnings were estimated to be $3.7 billion (2). Because of inflation and real increases in costs of services, the current annual cost of treatment will probably exceed $1.0 billion and the total economic impact will probably reach $5.7 billion.

Data defining the costs of specific components of therapy are not available; thus, such partitioning can only be speculative or inferential. It is clear, however, that supportive and rehabilitative therapy for patients with COPD are sources of great cost to the patient and to the public as well. Despite the magnitude of the problem and the amount of time and money expended in caring for patients with COPD, there is considerable controversy as to the overall results of therapy and whether or not treatment alters the natural history of the process (3-6). The role of many commonly used therapeutic modalities, both individually and in combination, remain to be defined. Of these, intermittent positive pressure breathing (IPPB) is perhaps the most costly and complex. The frequency and manner with which this form of therapy is applied vary widely and there is little or no substantiation of benefits or hazards. However, since IPPB was introduced almost 30 years ago, its use has increased at an extraordinary rate. This, in part, may be due to both physician and patient frustration at the failure of usual therapy to interrupt the relentlessly worsening disability; thus, the physician and patient anxiously seek any form of treatment that could possibly help. Often, both are convinced that IPPB offers relief not afforded by other treatment modalities despite there being no persisting measurable improvement in the usual indices of lung function.

The cost of IPPB therapy in the long-term management of patients with COPD is impossible to calculate. However, there are suggestions that the cost is considerable. If only one percent of the estimated 8.5 million persons with COPD were treated with IPPB at home, the cost for machines alone would be $30 million ($300-400/machine). Added to this would be an annual charge for maintenance and additional costs related to the necessarily close supervision required for patients using the devices. If, however, such devices are of substantial benefit in ameliorating or preventing disability and hospitalization, this cost may be easily justifiable. Because of the lack of specific information concerning the role of IPPB in the long term management of patients with COPD, and, because of the economic considerations related to this form of therapy, IPPB treatment in patients with stable COPD has been identified as a subject in need of careful examination (7). This study, therefore, is designed to answer many of the questions that have been raised concerning long term IPPB therapy. The information derived from this study should allow physicians and health policy administrators to apply this particularly expensive and complicated form of therapy in a much more efficient and economical way than is now being done.

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II. LITERATURE REVIEW

Studies that have attempted to evaluate the effectiveness of IPPB in patients with COPD are, in many cases, contradictory. It has been shown that blood gases improve and worsen (1-4), work of breathing increases and decreases (5-7), and patients are made better and worse (7-15).

The majority of the published data suggest that there is no added benefit from using IPPB to deliver bronchodilators in most patients with COPD. Nevertheless, it is possible that IPPB delivery of bronchodilator agents may be beneficial in patients with severe airways obstruction who are unable to coordinate with a manually-powered nebulizer or take a big breath. Wu and associates (16) reported that the delivery of bronchodilator aerosol by IPPB resulted in better removal of secretions and sustained improvement in patients who had excessive secretions. Improvement also occurred in patients whose respiratory insufficiency rendered them unable to coordinate hand nebulizer treatments. Cullen and colleagues (17) found that IPPB increased tidal volume and lowered arterial CO_2 tension in healthy subjects, but similar changes were seen in only 5 of 13 patients with severe emphysema. It is of interest that three patients who had increased ventilation during IPPB therapy were unable to reduce $PaCO_2$ by voluntary hyperventilation. This would support the suggestion that IPPB may be of value in certain patients

Ayres and co-workers (6) found that more mechanical work was performed while taking IPPB if the patient actively led the apparatus, but the amount of active work approached zero if the patient was completely relaxed. Sukumalchantra and associates (7) found that inspiratory work was far in excess of that generated during normal breathing. This appeared to result from exertion of an active expiratory effort before inspiratory flow ceased, and they postulated that this forced expiration resulted in potentiation of airway collapse in patients with COPD. This is in accord with the demonstration by Jones and colleagues (5) of an increase in expiratory airflow resistance with air trapping and increased FRC, when, in normal subjects the pressure-flow pattern present in patients with severe COPD was simulated by IPPB. These investigators also observed that IPPB failed to improve ventilation in about half of their patients, and when large cycling pressures were used, the IPPB became progressively more detrimental and, in fact, intolerable in severely obstructed subjects. They suggested that air trapping may have occurred in these patients. Others have suggested that this can become so severe that effective ventilation is decreased and IPPB therapy becomes intolerable (18-20).

Few studies have evaluated the benefits of long-term IPPB therapy in patients with COPD. Comparable decreases in dyspnea, cough, and volume of sputum (when present) were observed in ambulatory patients with COPD after two-week periods of treatment with bronchodilator aerosols generated either by an O_2 source or by an IPPB apparatus (10,11), and no significant

change in forced expiratory volumes or blood gases was found in patients who had been treated with IPPB for 6 days (21). Emirgil and co-workers (22) found that none of the various modalities of treatment, in common use in the management of patients with COPD, including IPPB, affected the deterioration of function or afforded any benefit to patients with COPD over a period of 1 year. Curtis and associates (23) followed a large number of patients with COPD, 78 of whom were treated with IPPB, for 4 years. When patients matched for FEV_1 were compared, there were as many deaths in the group with IPPB, and the rate of deterioration in FEV_1 was twice that of patients who were not treated with IPPB. They concluded that the chronic use of IPPB did not improve airflow resistance and that it may even have been detrimental. Cherniack and Svanhill (24) have reported a comparison of the long term effects of IPPB and air compressor to deliver a bronchodilator aerosol in 121 patients with severe airways obstruction (maximal mid-expiratory flow less than 30 percent of predicted). There were no differences in mortality, hospitalizations or days in hospital, and rate of deterioration of pulmonary function for the 2-3 year period of evaluation. In addition, although all groups demonstrated increases in residual volume and functional residual capacity, these changes were significantly greater in patients receiving IPPB. This potentially detrimental effect of IPPB was also suggested by the work of Motley and associates (9) who, after one week of IPPB therapy, demonstrated an elevation of RV and TLC in 8 of 10 patients who initially did not have gross overdistention (RV/TLC 35 percent) and in 8 of 19 patients with more severe overdistention. Finally, the possible effect of IPPB on the quality of life in COPD patients should also be considered. COPD patients are restricted in their capacity to work, exercise, and enjoy the normal activities of daily living. They suffer from increased depression, anxiety, and concern over bodily function. Some even show signs of neuropsychological deficits. If IPPB can be shown to improve clinical status in these areas, its usefulness as a treatment modality would be recognized.

In summary, although the majority of reported evaluations of IPPB therapy have not found it superior to other means of delivering aerosols, a clear cut answer as to its role is still not possible for the following reasons:

1. often, the number of subjects was small;
2. the groups were very heterogeneous;
3. subjects were not always randomized;
4. precise description of the manner in which IPPB was administered was usually not reported;
5. the patients' clinical and functional status were poorly defined;
6. the patients studied were so severely ill that no therapy could be demonstrated to be beneficial.

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III. OBJECTIVES

A. Primary Objectives

The following primary objectives have been established for this study:

1. To determine the relative effects of long term IPPB and compressor powered nebulizer treatments when used as an adjunct in the comprehensive care of ambulatory patients with COPD.

   a. To determine the relative effect of the devices on pulmonary function (e.g., FEV_1, TLC and arterial blood gas data).

   b. To determine the relative effect of the devices on the frequency, duration and reason for hospitalization.

   c. To determine the relative effect of the two devices on the quality of life.

   d. To determine the relative effect of the two devices on exercise performance.

   e. To determine the reasons and rates of attrition from the assigned treatments.

2. To determine the relative safety of long term IPPB and compressor powered nebulizer treatment when used as an adjunct in the comprehensive care of ambulatory patients with COPD.

   a. To determine the relative effect of the two devices on mortality.

   b. To determine the relative effect of the two devices on the incidence of infections.

B. Secondary Objectives

Secondary objectives for this study are listed below. Failure to achieve these objectives would not detract from the overall value of the study.

1. To determine the relative effect and safety of IPPB and compressor powered nebulizer in the following subgroups of patients:

   a. patients with airflow obstruction of various degrees;

b. patients from different age groups;

c. patients with various degrees of reversibility of airflow obstruction (defined on the basis of acute response to an inhaled bronchodilator);

d. patients with and without emphysema;

e. patients with and without carbon dioxide retention.

IV. STUDY DESIGN

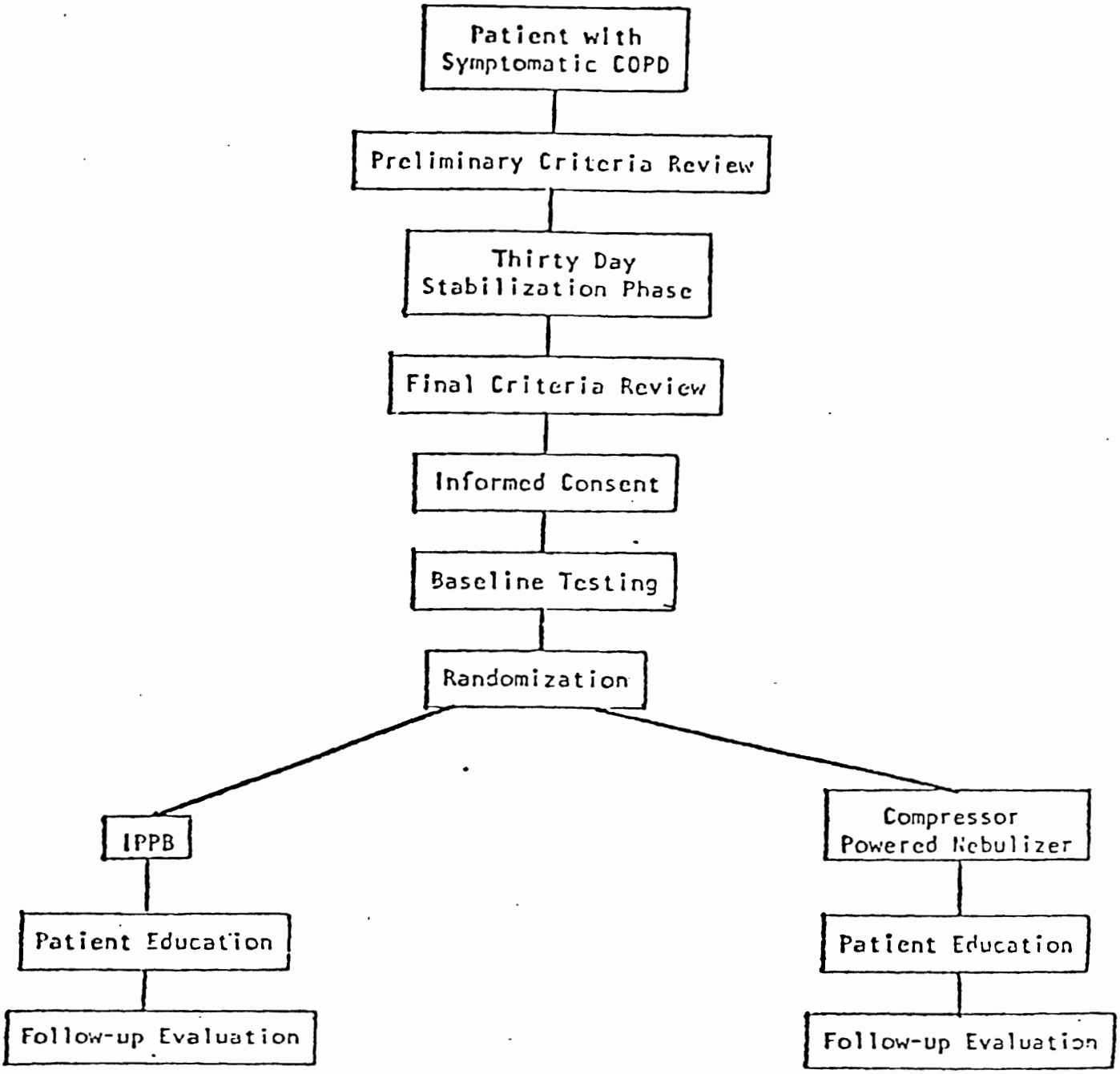
A. Overview

The Intermittent Positive Pressure Breathing (IPPB) study is a cooperative randomized controlled clinical trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI). There are five clinical centers, a pathology center, a data center, and the NHLBI program office. Each of the participating centers will adhere to a common protocol that defines entry and exclusion criteria, patient management, and evaluations. The primary objectives of the study are to determine the relative effects and safety of long term IPPB and compressor powered nebulizer treatment when used as adjuncts to the comprehensive care of ambulatory patients with COPD. Although treatment cannot be blinded, patients and physicians will be blinded to the cumulative results of the study during patient recruitment and follow-up. Prior to entry, patients must provide informed consent and a willingness to participate in the study.

Patients who meet preliminary entry criteria will enter a 30-day stabilization period during which standardized therapy (exclusive of IPPB or compressor nebulizer) will be initiated. At the conclusion of this period, final entry criteria will be reviewed by the clinical center and the data center (Figure 1). The study will again be discussed in detail with the patient who will be asked to sign a more comprehensive informed consent (Section VIII.C) for the full study period. Patients who meet the criteria and who agree to continue will undergo a baseline evaluation and then be assigned at random by the data center, to either the IPPB group or compressor nebulizer group.

Each patient will be followed for 30-36 months or until death or withdrawal from the study. Patients who, after being randomized, deviate from the study protocol will continue to be considered as study patients.

FIGURE 1. SEQUENCE OF ENROLLMENT AND EVALUATION



Thus, patients who miss scheduled follow-up visits or who lose interest in the study nevertheless remain study patients, regardless of whether or not they remain on prescribed therapy. It is important, therefore, that all patients entered into the study be highly motivated and that, once randomized, the treatment center maintain the patient's motivation. If a patient does miss one or more routine follow-up visits, every attempt should be made to conduct at least the 6 month evaluation.

The study duration will be 60 months. Patients will be enrolled during the first 30 months All patients who enter the study will be followed for 30-36 months. Follow-up examinations will be made according to the following schedule through the period of observation (see Section V.B.).

1. Weekly: During the first month after randomization, each subject will receive a weekly home visit for supervision of therapy, evaluation of clinical status, and monitoring of adherence to the assigned treatment regimen.

2. Monthly: After the first month, each patient will receive a monthly home visit for supervision of therapy, evaluation of clinical status, monitoring adherence to the assigned treatment regimen and quality of life measurements. Every third month the home visit will be replaced by a visit to the clinic for the same purposes plus a spirogram.

3. Quarterly: Clinic visits for limited follow-up evaluation including spirometry.

4. Semiannually: Clinic visits for intermediate follow-up evaluation including quality of life studies, blood gases, and spirometry.

5. Annually: (Baseline, 3, 12, 24, 36 months) Clinic visits for major follow-up evaluation including pulmonary function tests, exercise tolerance, etc.

It is not necessary for the clinical center to assume full medical responsibility for each study patient as long as there is full cooperation between the clinical center and the other care providers to ensure the protocol is followed. General guidelines are outlined in the protocol for respiratory as well as overall care. (See Section V.C.)

Variables to be measured include pulmonary function (diffusing capacity, single breath nitrogen washout, plethysmography, spirometry, lung mechanics, exercise testing, and arterial blood gases), quality-of-life evaluation, frequency and duration of hospitalization, frequency of respiratory infection, and mortality. When available, autopsy data will be obtained with special emphasis on lung pathology. All data required by the protocol will be collected by the investigators and forwarded to the Data Center for processing within a prescribed time schedule. Descriptions and time schedule for the specific data to be collected in the study are given in Section V. The investigators will

not be provided with cumulative data summaries of the results of therapy during the recruitment phase or follow-up phase of the study.

Study subjects may require hospitalization during the clinical study. When illness requires interruption of the assigned treatment regimen, the subject will be returned to the assigned regimen as early as possible in accordance with good clinical practice, and the schedule of follow-up examinations will be resumed without alteration of due dates. If a subject is unable to return to the assigned treatment regimen, every effort will nevertheless be made to carry out the next scheduled semi-annual examination.

B. Sample Size

The primary objective of the study is to estimate the relative effects of IPPB and of compressor nebulizer for various outcomes of treatment including measures of pulmonary function, incidence of illness and death, and general well being of the patient. These comparisons of treatment groups will employ differences in average values during the follow-up period for some types of outcomes (e.g., incidence of hospitalization), and differences in rates of change for other types of outcomes (e.g., measures of pulmonary function), as indicated in Section VI, Data Analysis.

A judgment has been made that a difference between the two treatment groups of 20 percent for most types of outcomes would have clinical importance, and that the sample size should be adequate to detect differences of that magnitude with a power of 90 percent, using a two-sided test of statistical significance at the 5 percent level. Treatment groups will be of equal size in order to yield maximum power.

Information on the natural history of COPD is sparse with respect to rates of progression and their variability among individual patients. This situation will persist until data to be collected during the 3 year follow-up become available. An exception is that data are available on long-term changes in some measures of pulmonary function, notably $FEV_{1.0}$. Fletcher et al. (1) report that $FEV_{1.0}$ declined at an average rate of 30 milliliters per year in a large group of employed men aged 30-59 and that the standard deviation of the regression of $FEV_{1.0}$ for individual subjects was 20 ml., based on semiannual measurements over a period of 8 years. It is expected that the rate of decline will be somewhat larger in the present study because the subjects will have more severe obstruction, and that the standard deviation of the rate will be larger because the measurements will be made quarterly over a period of only 3 years.

It is estimated that to detect a 20 percent difference between treatment groups in rate of decline of $FEV_{1.0}$ under the conditions specified above (90 percent power, 5 percent significance level), the present study of two equal-sized groups must include a total of 1,050 subjects if the mean rate

of decline in FEV_1 is 30 ml. per year and the standard deviation of the rate is 30 ml; or 600 subjects if the mean rate is 40 ml. and the standard deviation is 30 ml. These estimates do not take into account the loss of study subjects to follow-up due to death or discontinuation of treatment for other reasons. A sample of 1,000 subjects should be adequate if losses to follow-up can be kept to a minumum.

C. Study Personnel

1. Clinical Centers

University of Manitoba, Winnipeg, Manitoba
Principal Investigator: Nicholas R. Anthonisen, M.D.
Co-Investigator: Vincent Taraska, M.D.
Chief Nurse: Lynda Mendella, R.N.

University of Oklahoma, Oklahoma City, Oklahoma
Principal Investigator: David C. Levin, M.D.
Chief Nurse: Brenda Smith, R.N.

Loma Linda University, Loma Linda, California
Principal Investigator: John E. Hodgkin, M.D.
Co-Investigators: Glen N. Gee, R.R.T.
Eileen Zorn, R.N., M.S.

Baylor College of Medicine, Houston, Texas
Principal Investigator: Paul M. Stevens, M.D.
Chief Nurse: Ruth Abeles, R.N.

University of California, San Francisco, California
Prinicipal Investigator: Philip C. Hopewell, M.D.
Co-Investigator: John W. Little, M.D.
Chief Nurse: Joan Turner, R.N., M.S.

2. Data Center

George Washington University, Bethesda, Maryland
Director: Dean E. Krueger, M.S.
Co-Director: Elizabeth C. Wright, MPH

3. National Heart, Lung, and Blood Institute (NHLBI)

Director, Division of Lung Diseases: Claude Lenfant, M.D.
Administrator: Richard J. Sohn, Ph.D.
Statistician: David DeMets, Ph.D.

4. Pathology Center

University of British Columbia, Vancouver, British Columbia
Director: William H. Thurlbeck, M.D.

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   William F. Miller, M.D.
   Louis Vachon, M.D.
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V. STUDY PROTOCOL

A. Patient Selection

All patients who have symptomatic COPD (including at least one of the following: chronic cough, sputum production, or dyspnea) and who are referred to one of the clinical centers will be reviewed for admission to the study. Patients who meet entry criteria (a-d below) will be considered eligible for the stabilization phase of the study. After the completion of the stabilization phase, all patients who satisfy all of the entry criteria and have none of the exclusion criteria will be entered into the study.

1. Entry Criteria

   a. All patients must have a clinical diagnosis of COPD.

   b. All patients must be 30-74 years of age.

   c. All patients must have a prebronchodilator $FEV_{1.0}$ of less than 60% predicted and a prebronchodilator $FEV_{1.0}/FVC$ ratio of less than 60%.

   d. All patients must be capable and willing to participate in the clinical study, and:

      (1) be ambulatory and capable of sitting on and pedaling a bicycle ergometer;

      (2) live close enough to the Center to be accessible for home and clinic visits;

      (3) provide informed consent.

   e. All patients must have completed a 30-day stabilization phase on the standard regimen. (See Section V.C.)

   f. All patients must satisfy the following pulmonary function measurements twice, not less than 1 week or more than 90 days apart, while on the standard regimen (see Manual of Operations for protocols).

(1) the prebronchodilator $FEV_{1.0}$ is less than 60% predicted and the prebronchodilator $FEV_{1.0}/FVC$ ratio is less than 60%.

(2) the $FEV_{1.0}$ must be reproducible; that is agree within 0.2 liter or 15%, whichever is greater.

g. All patients must demonstrate reliability during the stabilization period. Reliability will be established by adherence to the treatment program as documented by pill counts (having taken at least 60% of the prescribed theophylline preparation) and maintenance of appointments for baseline evaluations (at least two visits will be necessary).

2. Exclusion criteria

The presence of any one of the following characteristics before or during the stabilization period will exclude a patient who otherwise meets the study requirements:

a. In response to 250 micrograms of inhaled isoproterenol, the FEV_1 increases to 80% or more of the predicted value or the FEV_1/FVC increases to 75% or more.

b. There is radiologic evidence of significant complicating lung disease.

c. The total lung capacity is less than 80% of the predicted value.

d. There are other illnesses that could be expected to alter the quality or duration of life. A list of examples follows which was in no way intended to be exhaustive.

1) malignant neoplasms (excluding basal cell carcinoma);

2) cardiac disease defined by cardiomegaly (cardiothoracic ratio greater than 0.5), angina pectoris, clinical or electrocardiographic evidence of myocardial infarctions within the last 6 months.

3) serum creatinine of more than 1.8 mg/dl;

4) significant neuromuscular dysfunction including evidence of cerebrovascular accident;

5) evidence of active liver disease;

6) Insulin dependent diabetes.

e. The patient must not have been taking either propranolol or cromolyn sodium during the 30 days of stabilization.

f. The patient cannot have used home IPPB or compressor nebulizer during the 30 days of stabilization. In addition, such devices cannot have been used for more than 30 continuous days in the 6 months prior to identification.

g. The patients can neither have used home oxygen supplementation during the 30 days of stabilization or used such treatment for more than 12 hours a day for 30 continuous days in the 6 months prior to identification.

In addition, the patient cannot, on initial evaluation, meet the criteria for home oxygen administration listed in Section V,D,1,g.

h. The patient cannot be pregnant.

3. Quotas

a. At least 25 percent of subjects will have moderate airflow obstruction (FEV_1 between 40% and 60% of predicted).

b. At least 25 percent of subjects will be severely obstructed (FEV_1 less than 40% predicted).

c. At least 20% of subjects will show evidence, at least once, of reversibility ($FEV_{1.0}$ will increase at least 15% with acute bronchodilator administration).

B. Stabilization Phase

All patients considered as potential candidates for the study require a 30-day stabilization phase prior to baseline studies. The definition of clinical stability remains the judgment of the attending physician. In the event of an acute illness during this time, the patient will be treated with appropriate therapy. Following the acute illness, either baseline or repeat $FEV_{1.0}$ measurements must agree within 0.2 liter or 15% of previous value, whichever is greater. During the stabilization phase:

1. Standard treatment regimen is to be applied (Section V.C.1.) with the following specific restrictions:

a. no propranolol or cromolyn sodium;

b. no home use of IPPB or compressor nebulizer;

c. no home use of oxygen supplementation.

2. Pre- and post-bronchodilator measurement of $FEV_{1.0}$ and FVC must be obtained after the patient has been on standard treatment for at least one week. A second set of measurements must be obtained not less than a week or more than 90 days from the first (See Manual of Operations.)

C. Study Phase

The Manual of Operations provides standardized methods and examples of data forms for all studies.

1. Baseline Studies

Baseline studies will be made on all patients who complete the 30 day stabilization and satisfy all entry criteria with no exclusion (Section V.A.). The schedule of the baseline studies may be at the discretion of the clinical center except where specifically noted. The baseline studies will include:

a. complete history and physical exam (see forms 704 and 705);

b. laboratory studies (see forms 704, 712, 713, and 714);

(1) hemoglobin

(2) hematocrit

(3) total white blood cell count

(4) peripheral eosinophil count

(5) semiquantitative estimate of sputum eosinophils

(6) plasma theophylline level

(7) culture of sputum

(8) chest roentgenogram

(9) electrocardiogram

c. pulmonary function tests (see form 710);

(1) diffusing capacity (single breath)

(2) single breath N_2 washout: Phase III slope

(3) plethysmography (pre- and post-bronchodilator): functional residual capacity (FRC), thoracic gas volume (Vtg), airway resistance (Raw)

(4) spirometry (pre- and post-bronchodilator) FVC, $FEV_{1.0}$, IC.

(5) lung mechanics: lung recoil (Pel) for 100, 90, 80, and 70% TLC and at FRC.

d. Exercise testing (see form 711)

Progressive multi-stage tests on cycle ergometer; heart rate, maximum exercise level.

e. Quality of Life Measurements (see forms 730, 731, 732 and 733).
(1) Sickness Impact Profile (SIP)

(2) Katz Adjustment Scale (relative's portion only)

(3) Profile of Mood States (POMS)

(4) Recent Life Changes Questionnaire (RLCQ)

f. Training and instruction of patient to disease and home treatment.

2. Randomization

Upon completion of the Baseline Studies, all patients will be randomized into the IPPB or compressor nebulizer treatment groups by the Data Center (See Section VIII. C).

3. Follow-up

The follow-up of all patients will occur by home and clinic visits. The schedule for all visits will begin at the time IPPB or CN is started. Visits not made within specified time limits will be recorded as a missed visit.

a. Home Visits

Home visits will be made by study personnel once per week for the first month and then once per month (except for months of clinic visits) for the 36-month study to assess clinical status and treatment compliance (see form 716).

(1) Symptomatic and physical exam

(2) Review of therapeutic regimen

(3) Evaluation of treatment compliance

(4) Assessment of medical status

(5) Measurement of plasma theophylline (per schedule)

(6) Collection of equipment cultures (per schedule)

(7) Respiratory rate during treatment.

b. Clinic Visits

(1) All scheduled clinic visits are shown in Table 1 (see Form 717).

(2) Emergency or unscheduled hospital admission and treatment should be under direction of a study physician as far as possible. Data to be collected include (see form 720):

(a) History and physical examination

(b) Laboratory studies

(c) Treatment

(3) Treatment with antibiotics should be reported on Form 727.

c. Autopsy

Every attempt should be made to obtain a post-mortem examination of the lungs and heart on all study patients who die during the study. All post-mortem lung and heart material will be forwarded to the Pathology Center in Denver, Colorado.

D. Patient Management

1. All patients

a. Oral theophylline

All patients who can tolerate oral theophylline should receive a long acting (sustained release) pure theophylline preparation. The initial dose in most cases should be 6 to 8 mg/kg every 12 hours unless the patient has a prior history of theophylline intolerance in which case an even lower initial dose may be used. Plasma or serum concentrations (1-3) hour prior to the next dose (trough level) should be in the range of 10 to 15 micrograms per ml when measured 10 to 14 days after starting treatment. These doses should be expected to produce peak levels that should not exceed 21 micrograms per ml. The dose will be adjusted to meet these criteria whenever patient tolerance permits. The analysis will be performed using the high pressure liquid chromatograph method or an equivalent method. Patients will be instructed concerning the possible side effects of theophylline and asked to record any indications of toxicity on the treatment log. If toxicity occurs, the dose of theophylline will be adjusted downward and plasma or serum levels will be measured.

Patients who cannot achieve adequate plasma or serum theophylline levels without side effects (e.g., nausea, arrhythmias) may be given oral $Beta_2$ - type bronchodilators.

b. Inhaled beta adrenergic agents

All patients will be supplied with freon-powered metered dose containers of metaproterenol. This will be used during the stabilization phase and when needed to supplement the bronchodilator or the powered nebulizer. The dose is 200-400 micrograms administered no more than every 3 hours.

c. Antibiotics

The indications for the use of antibiotics are as follows:

(1) Documented bacterial pulmonary parenchymal infections (indicated by leukocytosis, fever, abnormal chest roentgenogram, and the presence of significant bacteria

In the sputum). Antibiotic selection will be based on the usual bacteriologic and clinical criteria.

(2) Presumed or proven bacterial bronchitis (indicated by increased sputum volume, increased viscosity or change in color of sputum without evidence of parenchymal infection on chest roentgenogram, if done). In this circumstance, either ampicillin 500 mg. q.i.d., tetracycline 250 mg. q.i.d., erythromycin 250 mg. q.i.d., Keflex 500 mg. q.i.d. or Septra one tablet b.i.d. for 7 days may be used empirically. If infection does not respond to this empiric choice of antibiotics, bacteriologic evaluation must be undertaken and antibiotic choice based on bacteriologic and clinical criteria.

d. Corticosteroids

Chronic corticosteroid treatment will be used only for patients who are found to have symptomatic and/or physiologic improvement. The determination of improvement will be made by the individual physician caring for the patient. All patients who continue to be significantly symptomatic (especially those who have cough and/or wheezing at night associated with blood and/or sputum eosinophilia) while being treated with an optimal therapeutic regimen will be given a trial of oral corticosteroids unless there are specific contraindictions. The trial will consist of prednisone 40 mg daily for 1 week. In responsive patients, corticosteroid treatment will be continued at the lowest oral or inhaled dose that will maintain improvement.

e. Diuretic agents

Diuretics may be used to treat left and/or right ventricular failure, and/or systemic arterial hypertension.

f. Digitalis

Digitalis preparations may be used to treat left ventricular failure or supraventricular arrhythmias.

g. Oxygen supplementation

To qualify for supplemental home oxygen, patients must have a PaO_2 of less than 55 mm Hg measured twice, at least 2 weeks apart, while clinically stable, being maximally treated.

Oxygen will be prescribed at 1-4 liters/minute for at least 18 hours/day if possible.

Patients who are to begin O_2 must be reevaluated with full baseline studies before (or soon after) starting O_2.

h. Expectorants and bland aerosols may be used by study patients at the discretion of the primary physician. The aerosol must be administered by whichever device is being used in the study. However, bland aerosols should not be inhaled on days when pulmonary function testing is to be performed. Acetylcysteine will not be used for study patients.

i. Chest physiotherapy and postural drainage.

Postural drainage, with or without chest percussion, may be used whenever it is considered beneficial by the primary physician.

j. Exercise Training

Graded activity training (see Manual of Operations) and regular exercise will be encouraged for all study patients.

k. Education

All patients will complete the educational program. The objectives and content of these sessions are in the Manual of Operations.

2. IPPB Group

a. Device

The IPPB device used for all study patients will be the Bennett AP-5 with the Bennett breathing circuit and nebulizer. These units will be modified and contain an elapsed time meter to indicate the total time in use.

b. Nebulized bronchodilator

Metaproterenol will be the nebulized agent used for all study patients where provided. The dose prepared for each treatment will be 5-25 mg. of metaproterenol (5% Alupent) diluted in 2.5 ml of sterile water administered three or four times a day. The treatment will be continued until all the medication has been aerosolized.

c. Tidal volume will be at least 15 ml/kg body weight or at least 75% of the inspiratory capacity if the inspiratory capacity is less than 15 ml/kg. The device pressure required to deliver the calculated tidal volume will be determined following randomization. Tidal volume will be measured and, if necessary, the pressure adjusted at each home visit.

Patients will be instructed to exert the minimum effort necessary to begin inspiration, to allow passive lung inflation and

to exhale to functional residual capacity before again inhaling. Detailed patient instructions are contained in the Manual of Operations.

Compressor Powered Nebulizer Groups

a. Device

The Bennett compressor will be used by all study patients. The Bennett nebulizer identical to that used with the IPPB device will be used. An elasped time indicator will be attached to the compressor to indicate total time used.

b. Nebulized bronchodilator

Metaproterenol, identical in dose and dilution to that used for the IPPB group, will be utilized.

c. Tidal volume and breathing pattern

The patient will be coached to breathe with a tidal volume of at least 15 ml/kg body weight or 75% of inspiratory capacity if the inspiratory capacity is less than 15 ml/kg. Tidal volume will be measured at each home visit and patient coaching reinforced if necessary.

4. Management of Acute Exacerbations or Complications

During acute exacerbations, appropriate therapy provided by the investigators will not be restricted, but all measures must be carefully documented. (See Manual of Operations for forms).

E. Data Requirements

In order to assure uniform collection of data by all participants, all observations and measurements will be made under specified conditions and at predetermined time intervals, recorded on appropriate data forms, and forwarded to the Data Center for statistical analysis. Data forms and precise methodology are detailed in the Manual of Operations.

Technicians and nurses shall receive formal workshop training before initiation of this study. The emphasis of these workshops will be standardization of testing procedures, techniques, and measurements. Frequent on-site visits at each institution will be made to insure that the standard protocols are being followed.

1. Complete history and physical examinations and routine laboratory studies.

   a. Frequency: Baseline and every 3 months or as scheduled (see Table 1)

   b. Procedures: As specified

   c. Measurements: See standard history questionnaire, physical examination form, and routine lab form. (Manual of Operation)

2. Arterial Blood Gases and Hematocrit (per schedule).

   a. Frequency: Baseline, 3, 6, 12, 18, 24, 30, 36 months.

   b. Procedures: Arterial puncture method. Aseptic technique with heparinized syringes and following suggested guidelines.

      (1) Rest sitting for at least 5 minutes

      (2) Local anesthesia (as locally prescribed)

      (3) Radial artery puncture

   c. Measurements: Iced or refrigerated sample tested within 30 minutes of collection for PaO_2, $PaCO_2$, and pH.

3. Pulmonary Function Tests

   As nearly as possible, all subjects will be tested under similar conditions. Spirometry and plethysmography will be performed with no IPPB or compressor nebulizer treatment at least 6 hours prior to testing. If patients forget or cannot tolerate this withholding period, the time, in hours, elapsed since the medication(s) was taken until spirometry (before bronchodilator challenge) begins will be recorded and forwarded to the Data Center.

a. Frequency:

(1) Complete Studies (Baseline, 3, 12, 24, 36 months)

(a) D_LCO

(b) N_2 washout, single breath (Slope, Phase III)

(c) Plethysmography

(d) Spirometry

Bronchodilator challenge

Wait 15 minutes

Plethysmography

Spirometry

(e) Lung mechanics

(f) Exercise testing (includes arterial blood gases)

(2) Interim Studies (6, 18, 30 months)

(a) Arterial blood gases

(b) Spirometry

Bronchodilator challenge

Wait 15 minutes

Spirometry

(3) Spirometry Only: pre and post bronchodilator - (9, 15, 21, 27, 33 months)

b. Methods, Procedures, and Measurements

(1) Diffusing Capacity (D_LCO) maneuver

(a) Methods: A single breath carbon monoxide diffusing capacity (D_LCO) maneuver will be performed. A Collins automated (Gaensler-Smith) bag-in-box-spirometer system will be used. An infrared CO analyzer and a thermal conductivity He analyzer is included.

(b) Procedure: With subject seated, and nose clipped.

1) The subject exhales maximally and signals when the "lungs are empty."
2) The automated valve sequencing is activated.
3) The subject inhales the test gas to TLC and breath holds. (The pre-set breath holding time will be 9.5 seconds).
4) The patient then exhales rapidly. The washout volume will be set at 750 ml. (If the vital capacity is less than 1.2 liters, the washout volume may be reduced to 600 ml.)
5) The next 650 ml of expired gas (alveolar sample) is collected. In patients with low vital capacities, the alveolar sample volume may be reduced as necessary to as low as 400 ml.)
6) The test is repeated twice with at least a 3-minute room air washout between tests.

(c) Measurements: The alveolar sample is immediately analyzed for CO and He. Diffusing time and inspired vital capacity (corrected to STPD) are calculated from the spirometer measurements. Alveolar volume will be calculated from the single breath He dilution ratio. D_LCO is calculated for each test. Valid results from three maneuvers will be reported in ml/min/mmHg.

(2) Single Breath Nitrogen Washout

(a) Methods: A single breath technique will be employed that meets the general guidelines set forth in the July, 1973, publication distributed by the Division of Lung Diseases, National Heart, and Lung Institute: Suggested Standardized Procedures for Closing Volume Determinations (Nitrogen Method), prepared by Drs. Richard Martin and Peter Macklem. An external expiratory resistance is optional to control expiratory flow at or below 0.5 liters/sec.

(b) Procedures: With subject seated, nose clipped

1) Exhale to residual volume
2) Inhale 100% oxygen to total lung capacity
3) Without breath holding, exhale at 0.5 L/sec to residual volume
4) Repeat once after at least 5 minutes. (The vital capacities must agree within 10%.

(c) Measurements:

The Slope of Phase III, calculated as the percent N_2 change between 750-1250 cc exhaled from TLC, will be determined.

(3) Plethysmography

(a) Methods: A constant volume variable pressure plethysmograph will be used for both volume and airway resistance measurements. The techniques of DuBois and co-workers will be employed. (Journal of Clinical Investigation 35:322, 1956 and ibid 35:327, 1956). Shallow rapid breathing technique is essential.

(b) Procedures: The patient will be seated in the plethysmograph with nose clipped. The patient should be comfortable with both feet on the floor of the box, legs uncrossed. The mouthpiece of the pneumotach should be adjusted for comfort with chin slightly elevated.

(c) Measurements: The following values will be determined from the average of at least three maneuvers for each variable.

1) Functional residual capacity (FRC) - thoracic gas volume (Vtg) at end of normal expiration.
2) Airway resistance (Raw).
3) Vtg - volume at which Raw measured.

(4) Spirometry

(a) Methods: A volume displacement spirometer from which permanent tracings of volume and flow versus time may be generated.

(b) Procedures:

1) Forced expirations: Standing, nose clipped breathing on the spirometer, the subject inhales to TLC; the forced maximal expiratory maneuver to RV follows immediately for determination of FVC (which will be measured at least three times).
2) Slow vital capacity:
   a) from FRC, maximum inspiration to TLC, then slow exhalation to RV. Performed twice.
   b) from FRC, complete exhalation to RV, then inhalation to TLC. Performed twice.

(c) Measurements: All values in BTPS.. The data from three acceptable forced expiratory curves will be sent to the Data Center. These data are the FVC, FEV_1, and FEF. The $FEF_{25-75\%}$ and instantaneous flows at 75, 50, and 25% of the FVC will be measured on the best of the three curves only. This curve is defined as the one with the largest sum of FVC and FEV_1.

The slow VC is the largest of the recorded values. Inspiratory capacity (IC) is the larger of the two values.

(d) Bronchodilator Challenge: Bronchodilator challenge will consist of inhalations from RV of 250 micrograms of isoproterenol delivered by a freon propelled aerosol. This would be accomplished by two activations of the metered-dose cartridge inhaler in one breath from RV or one activation from FRC. (Each activation delivers a dose of 125 micrograms.) Approximately five seconds of breath holding should follow inhalation. Repeat testing commences 15 minutes after isoproterenol inhalation. Post-challenge testing begins with plethysmography on complete testing days and with spirometry on interim study days.

(e) Helium - Oxygen Spirometry ($He-O_2$)

Optional. Results are not reported to the Data Center. Guidelines in the appendix are suggestions only except that no more than three forced vital capacities should be performed to avoid patient fatigue.

(5) Lung Mechanics

(a) Methods: The technique outlined by Peter T. Macklem, National Heart and Lung Institute, Division of Lung Diseases Pamphlet, November 1974, Procedures for Standardized Measurements of Lung Mechanics, will be employed. Volume may be measured at the mouth by spirometer or in a variable volume plethysmograph. Expiratory pressure volume curves using a mouth shutter interrupt technique will be employed. Subjects will fast at least two hours before balloon placement.

(b) Procedures: After the esophageal balloon is positioned, the patient will be seated in the constant volume, variable pressure plethysmograph for measurement of FRC before connecting to the spirometer mouthpiece. If volume is measured by variable volume plethysmography, FRC and volume change will be determined in the box. Exhalation from TLC will be interrupted periodically by mouth shutter. The maneuver will be repeated at least three times.

(c) Measurements: Lung Recoil (Pel) will be determined for TLC, 90%, 80%, and 70% TLC and at FRC in cm H_2O. The volumes in mls from TLC to FRC will be reported.

4. Exercise Testing

a Methods: Pretest Conditions

Subjects must be fully recovered from any other studies. No food is to be eaten within two hours of testing. An accurately calibrated electromechanical cycle ergometer will be employed. The electrocardiograph (EKG) must be monitored continuously during exercise.

b. Procedures:

(1) resting, seated arterial blood samples
(2) Phase I - One Minute Increment Test

(a) Sequence
Begin cycle pedalling at 100 kpm. Workload is increased in 100 kpm increments each minute.

(b) Exercise End Points

1) symptom limited
2) heart rate (HR) 180/min or significant EKG changes

(c) Report to Data Center

1) HR, respiratory rate, and ventilation at each workload increment.
2) maximum exercise level

(3) Phase II - Steady State (SS) Exercise and Gas Exchange

Subjects must completely recover from Phase 1 before proceeding.

(a) Sequence

1) pedal for at least 4 1/2 minutes* at the prescribed metabolic load.
2) collect expired gases and measure inspired volume for the last minute of exercise.
3) draw an arterial blood sample after 4 1/2 minutes* of pedalling.

(b) Report to Data Center

HR	Rest and SS
f	Rest and SS
PaO_2	Rest and SS
$PaCO_2$	Rest and SS
pH	Rest and SS
V_E	Rest and SS
VO_2	Rest and SS
VCO_2	Rest and SS
VD/VT**	Rest and SS
$P(A-a)O_2$ mmHg**	Rest and SS

*Data to be collected at 3 min. This data to be reported if patient is unable to complete 4 1/2 minute study.

**calculated

5. Quality of Life Measurements

a. Frequency

(1) Sickness Impact Profile, Katz Adjustment Scale (relative's portion only); Profile of Mood States. Baseline, 6, 12, 24, and 36 months.

(2) Recent Life Changes Questionnaire - Baseline and every 12 months.

6. Autopsy

a. Frequency: When available.

b. Procedures:

(1) The coroner or medical examiner is notified when appropriate. If statutes do not require a medical examiner's autopsy, or if the medical examiner declines jurisdiction, the next of kin is approached for permission to conduct a postmortem examination.

(2) The heart and at least one lung will be removed from the thorax.

(3) One unopened lung, preferably the left, with the bronchus left long (cut flush with the tracheal carina) will be wrapped in plastic (i.e., saran wrap) and stored at about 4° C.

(4) Following whatever pathologic examination is required by the controlling pathologists including dissection and tissue samples, the remaining heart will be wrapped in plastic (i.e., saran wrap) and stored at about 4° C. The weight and sites of all tissue removed should be recorded and forwarded to the Pathology Center.

(5) The heart and lungs should be refrigerated until just before packing and shipping. The insulated package should include a number of blocks of ice in a sealed plastic bag. Not much ice is needed--the idea is to keep the organs at about 4°C and not to freeze them. The box should be wrapped in paper and marked FRESH BIOLOGICAL SPECIMENS: RUSH. THIS WAY UP. Appropriate stickers will be provided for each participating group. The container should then be taken to the small parcels office of the appropriate airline. When the package has been received by the airline and the flight number known, the participatory organization should phone Denver where a system will be set up to provide 5 day 8 a.m. - 5 p.m. coverage.

7. Compliance with Oral Theophylline Treatment

   a. Frequency: Monthly

   b. Procedures:

      (1) Record the amount prescribed at initiation of treatment and each subsequent change in prescription.

      (2) Record the quantity of the drug used between monthly home visits.

8. Compliance with Machine Treatment with Metaproterenol

   a. Frequency: Monthly

   b. Procedures:

      (1) Record the amount of drug prescribed per treatment at initiation of treatment and each subsequent change in prescription.

      (2) Record the quantity of the drug used between monthly home visits.

      (3) Record the meter reading (hours of use of the machine) at each monthly home visit so that time of use of the machine can be calculated.

TABLE 1 SCHEDULE OF EVALUATION

Parameter — Months	0	3	6	9	12	15	18	21	24	27	30	33	36
1. Pulm. Hx. questionnaire	X												
2. Symptom History	X	X	X	X	X	X	X	X	X	X	X	X	X
3. Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X
4. Laboratory Data:													
a. WBC	X												
b. Hct/Hb	X				X				X				X
c. Peripheral Eos. Count	X												
d. Plasma Theophylline Level (1)	X			X		X							
e. Sputum Eosinophils	X												
f. Sputum Gram Stain and Culture (3) (4)	X												
g. Equipment culture(2)													
5. Chest radiographs	X				X				X				X
6. ECG	X				X				X				X
7. Pulmonary Function Tests:													
a. A.B.G.	X	X	X		X		X		X		X		X
b. Spirometry	X	X	X	X	X	X	X	X	X	X	X	X	X
c. Body Box (lung vol. and airway resis.)	X	X			X				X				X
d. Exercise Test with gas exch. analysis	X	X			X				X				X
e. Lung compliance	X	X			X				X				X
f. Single breath N_2 test	X	X			X				X				X
g. DLCO	X	X			X				X				X
8. Quality of Life:													
a. Sickness Impact Profile (SIP)	X		X		X				X				X
b. Katz Adj. Scale (Relative)	X		X		X				X				X
c. Profile of Mood Statement (POMS)	X		X		X				X				X
d. Recent Life Changes Questionnaire (RLCQ)	X				X				X				X

(1) Also at home visit months 5, 17, and 29
(2) At home visit 1, 5, 11, 23, and 35
(3) Also during illness as needed
(4) Also when equipment culture is positive

VI. DATA ANALYSIS

A. Outcome Measures

The results of the trial will be analyzed and expressed in a number of ways. Outcomes will be assessed using the guidelines discussed below; however, other analyses and methods of evaluation may be found necessary during the course of the trial or at the time of the final analysis. In addition, the outcomes in the two treatment groups will be compared within and across the subgroups of patients defined in the statement of objectives (Section III).

Two major types of outcome relate to the efficacy and to the safety of treatment of COPD. Some outcome events will reflect both efficacy and safety whereas others may be related primarily to the safety of the therapy. For example, the inability of a particular treatment to retard deterioration of air flow would demonstrate a lack of efficacy and also reflect upon the long term safety of that treatment. Conversely, the incidence of infection possibly related to the use of the device would reflect predominately upon safety.

The specific outcome measures to be employed, and the manner in which the measurements will be used in these analyses are as follows:

1. Pulmonary Function

Specific measures of pulmonary function such as FEV_1, TLC, and arterial blood gas analyses will be obtained at predetermined intervals on all patients. For each function, for each patient, a trendline will be fitted to the successive observations on that patient, using least squares linear regression over time. The slopes of the measurements of the observations will then be used in comparative analysis for the two treatment groups. In addition, the algebraic difference of the observation at each follow-up visit from that at baseline will be employed in these analyses.

2. Hospitalization

For each patient, the frequency and duration of hospitalization will be evaluated. Analyses will be conducted by period of follow-up as well as cumulatively over the entire follow-up period for all patients.

3. Quality of Life

Data on quality of life at each follow-up evaluation will be compared to those at baseline.

4. Exercise Performance

The specific measures of exercise performance at each follow up observation will be compared to baseline performance using both algebraic differences, and where appropriate, rates of deterioration (i.e., slopes) in exercise function.

5. Mortality

The numbers of deaths, by cause of death, will be compared between the treatment groups, and survival curves for the treatment groups will be compared using life table methods.

6. Infections

The frequency of episodes of infections as reflected in prescription of antibiotics and number of exacerbations precipitated by infections will be compared between the treatment groups.

7. Treatment Termination

The number of patients who cannot continue on the assigned treatment because of worsening COPD status, including death from COPD and related causes, will be compared between the treatment groups.

The analysis of measures one through four will reflect primarily treatment efficacy, whereas those of measures five through seven will reflect safety.

B. Withdrawals from Treatment and Dropouts

Some patients may be forced to permanently discontinue therapy for reasons not related to the disease or its treatment. Such patients will be classified as withdrawals and will be defined on the basis of:

1. Development of severe intercurrent illness not associated with COPD or with its therapy.

2. Death due to other natural causes not associated with COPD or with its therapy.

3. Accidental death.

In addition, some patients may refuse to continue participation in the study for reasons not clearly related to their health. Such patients will be classified as dropouts and are defined on the basis of:

4. Loss to follow-up for any reason such as moving away from the center.

5. Refusal to participate in any follow-up.

Contact will be maintained with patients who withdraw or drop out, and every possible step will be taken to conduct the examinations called for at the end of the 3-year period of follow-ups.

Analyses of data on outcome of treatments will include or exclude data on patients who withdraw or drop out, depending on the purpose of the particular analysis and the possibility of bias related to incomplete follow-ups.

C. Interim Statistical Analyses

Interim analyses of incoming data will be made by the Data Center for each treatment group (not labeled). These interim reports will contain analyses of all outcome measures specified above. They will be reviewed on a regular basis by the Advisory Board.

If adverse effects emerge during the study, the study will be stopped or modified, the admission of new patients will be discontinued, and if warranted, treatment of previously entered patients will be discontinued. The Advisory Board will develop guidelines for study modifications as data become available. These guidelines will include proper statistical analyses of those possible indications of adverse effects which might lead to a change in the trial.

D. Monitoring Reports

In addition to the interim statistical analyses, routine monitoring reports will be generated by the Data Center and forwarded to all study participants. These monitoring reports will be used to assess the progress of the study and treatment center performance, using indices such as:

a. Patient recruitment rate
b. Dropout rate
c. Error rate in forms completion
d. Protocol violations

Such tabulations will be performed by treatment center, both cumulatively and for selected intervals. Treatment groups will not be identified in these monitoring reports.

E. Final Statistical Analyses

When all patients have been followed for 3 years, the Data Center will perform a final series of statistical analyses. The results of these analyses will be shared with the study group participants and used in publications to be prepared from the study. The primary analyses will consist of comparisons between the treatment groups on the outcome measures

specified above. In addition, the above outcome measures will be analyzed across various sub-groupings (where deemed possible) to satisfy the secondary aims of the study (See Section III). Other sub-group analyses will be performed as may be requested, but such results will be interpreted cautiously because of the multiplicity of comparisons and the consequent likelihood of occasionally encountering nominally significant differences.

In addition to the standard methods for the analysis of such data, other methods will also be employed in these final analyses. The most important alternate method will be the use of modified life table technique whereby withdrawals and dropouts will be included in analysis of the study cohort for the period over which they were receiving therapy.

VII. ORGANIZATIONAL AND ADMINISTRATIVE STRUCTURE

In this section the formal organizational aspects of the study are presented. The following subsections describe the most important formal units participating in the study. In addition, various subcommittees may be added to the organizational structure as needed. The formation of such committees will be the responsibility of the Steering Committee. This organizational structure is outlined in Figure 2.

A. Division of Lung Diseases, National Heart, Lung, and Blood Institute

The Division of Lung Diseases, (DLD), as sponsor of the study, will have primary responsibility for approving, implementing, and administering all aspects of the study with the units involved. The DLD personnel will include the Director of the Lung Division, the project office for the study, and other medical and biometric personnel as deemed necessary during the course of the study. The contracting officer is responsible for all administrative matters related to the award and conduct of the contract.

B. Steering Committee

The Steering Committee will consist of the principal investigator from each of the Clinical Centers, the Data and Pathology Center directors, and the DLD program officer. A chairman will be appointed by DLD. The Committee will be responsible for the scientific operation of the study. Its specific functions include the following:

1. To see that the program policy and protocol is carried out under the guidance of the DLD program office.

2. To review and analyze the progress of the program. This will include at least a final report.

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

C. Advisory Board

Selected members of the Pulmonary Disease Advisory Committee of the Division of Lung Diseases will serve on the Advisory Board to this collaborative program. Additional special consultants will be called to serve on the Board.

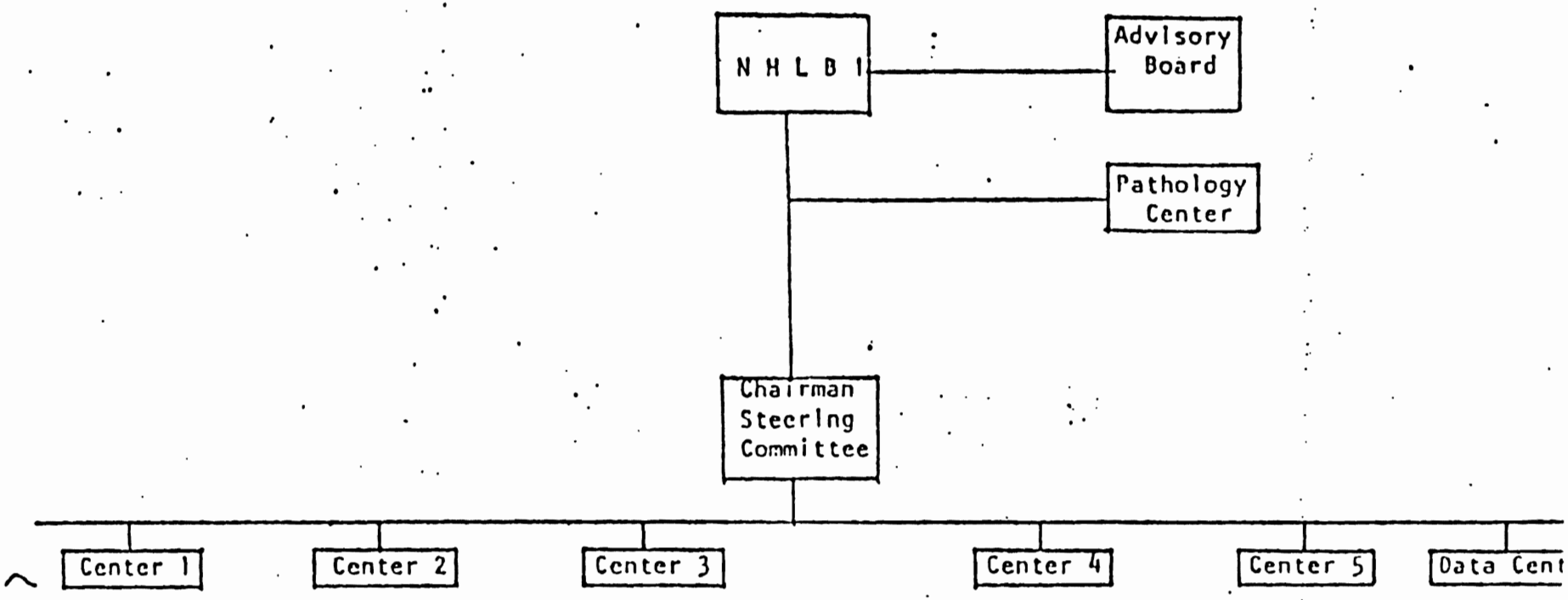

FIGURE 2

IPPB Clinical Trial
Collaborative Program

This Advisory Board will be responsible for advising DLD in all major operational decisions during the course of the study. To achieve this purpose, they will have access to all available data and can request specific information from the Steering Committee, the Pathology Center, or the Data Center through the program office. The specific responsibilities of the Advisory Board will be:

1. To review the protocol of the study.

2. To review any ancillary studies to ensure their purposeful impact upon the primary clinical study.

3. To assist in the resolution of problems referred to them.

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

5. To recommend possible changes in the protocol, organizational structure, operating procedures, or other aspects of the program to provide the study with improved capability of reaching its goals.

6. To monitor the performance of each of the participating centers and recommend remedial measures, if necessary, to stimulate performance.

D. Clinical Centers

The most important units in any scientific study are the units which perform the scientific work. The primary responsibility of the clinical centers will be to deliver the highest standard of medical care to the patients in both the IPPB and compressor nebulizer treatment groups. The clinical centers will also be charged with maintaining a high standard of investigative effort. They will be responsible for seeing that the scientific protocol is followed. In addition to other medical personnel involved in direct patient care, there will be a principal investigator who will be a member of the Steering Committee and be responsible to DLD for the ongoing operation of the study. Each participating clinical center will designate a study coordinator, who will see that appropriate forms are filled out and transmitted to the data center and will serve as a focal point for all telephone and written communications concerning patient data. The principal investigator, or his delegate, will be responsible for the quality control of the data.

E. Data Center

The data center will coordinate the collection, storage, and statistical analysis of all clinical data called for in the protocol. The data center will be represented on, and work under, the direction of the Steering Committee. The data center will not respond to requests for data other than reports called for by the protocol, except when authorized by DLD.

The responsibilities of the Data Center are:

1. Assist in the development of the study protocol and prepare to collect and analyze the data. They will:

   a. Cooperate with the Steering Committee in the development of the study protocol.

   b. Develop new or modified methods of analysis to meet the specific needs for data evaluation in this clinical study.

   c. Work with the investigators in the development and pretesting of forms and procedures for data recording and processing and assume responsibility for reproduction, distribution, and collection of forms.

2. Make a random assignment to IPPB or compressor nebulizer treatment for each patient who enters the study.

3. Train the necessary personnel and provide the facility to operate a data center for the study. This will include:

   a. Review of all data transmitted (on a standard form) by the clinical groups to ensure completeness and integrity.

   b. Ensure that participating centers meet requirements for standardization of observations, objective application of definitions, and other measures of quality control.

   c. Make reports evaluating the performance of the participating clinics.

   d. Process and store all clinical data and present in standard formats.

   e. Provide analyses (including statistical) of the data.

   f. Prepare interim technical and statistical reports.

   g. Collaborate with the clinical investigators in preparing reports of the study for publication.

F. Pathology Center

The Pathology Center will be responsible for the analysis of all pathological material collected for the IPPB Clinical Trial. Specifically, the Pathology Center shall:

1. Be responsible for the coordination of the preparation, storage, and shipment of post mortem lung pathologic specimens obtained from study patients as detailed in the IPPB Clinical Trial Protocol. This includes the following:

   a. Provide detailed procedures for study autopsy and specimen preparation.

b. Outline and coordinate methods for specimen packaging and shipment.

2. Analyze heart and lung specimens from the IPPB Clinical Trial (subject to availability) according to the methods outlined in the Manual of Operations.

3. Provide the Program Office and the Steering Committee of the IPPB Study with the analysis and interpretation of the pathological data.

VIII. POLICY MATTERS

A. 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 minimum of 200 patients) by each participating unit. Failure to adhere to the Protocol, Manual of Operations, or the patient load will be reviewed by the Project Officer and the Advisory Board. Major infractions or suboptimal performance will result in termination of contract support.

B. 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 admitted to the study unless there is a lack of informed consent, or lack of adequate therapeutic control. Furthermore, each participating center will supply the data center with Form 701 for all patients with a clinical diagnosis of symptomatic COPD who meet the definition of accessible patients.

Each participating center will assess its own preparation for applying the protocol to clinical patients. The protocol will be applied to every patient who enters the study and all patient data collected will become part of the total patient data pool once the center begins the study.

The principal investigator is 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 postmortem protocol.

C. Informed Consent

The policy of the Department of Health, Education, and Welfare 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 HEW 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 program office prior to the initiation of the study. This policy specifies that an informed consent must be obtained from all patients prior to treatment assignment.

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. A recent editorial suggests that informed consent may be "uneducated" consent. It may be possible, after an explanation with no coercion, to obtain a signature on a document that would satisfy the review committee. However, the reality of the situation 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 human rights committee. However, the following components must be incorporated into the informed consent of each center of this study;

1. I understand that the study is designed to compare the value of the two devices, the Intermittent Positive Pressure Breathing (IPPB) machine and Compressor Nebulizer (CN), in the treatment of my diagnosed condition of Chronic Obstructive Pulmonary Disease.

2. I understand that I have a 50% chance of receiving IPPB and a 50% chance of receiving CN. The best form of treatment is unknown. The device I receive will be determined by an independent research center and not my doctor.

3. I understand that before my assignment to a device is made, I will be carefully observed for 30 days on a standard treatment program without the use of IPPB, or CN, unless my physician concludes that going without these treatment modalities will be harmful.

4. I understand that if I participate in the study, my doctor will have more detailed information about my individual disease than is usually available and I will receive more medical and nursing care than usuall given. Costs for this extra care will not be billed to me.

5. I acknowledge that I have been provided with a full explanation of the procedures to be followed in the study, of the potential risks and benefits of the alternative modes of treatment. Among the potential benefits that have been described to me are slowing of deterioration of pulmonary function, greater exercise tolerance, lessening of pulmonary symptoms, and more intensive diagnosis and treatment.

6. I understand that several kinds of tests will be done at intervals during the study. Although the likelihood of life threatening complications are remote, some possible side effects of these tests may be uncomfortable and are mentioned below:

   (a) Catheterization, the insertion of a small tube into the artery will be required for the exercise test. If such catheterization should result in formation of a blood clot, surgery may be necessary to remove the clot from the artery.

   (b) A bicycle exercise test will cause shortness of breath and fatigue and may cause an irregular heart rate. An exceedingly rare complication is the development of an abnormal heart rhythm, with ineffective heart beat (cardiac arrest). This may require drugs intravenously, electrical shock, or chest compression with assisted breathing to convert the heart back to normal beat. Death during stress testing has occurred in approximately one out of 10,000 tests performed (and this was principally in heart disease patients).

   (c) Tests will be given and personal questions asked that will require several hours to answer. These tests may cause fatigue.

   (d) One of the breathing tests requires that I swallow a small balloon (that is attached to a very narrow tubing) into my esophagus (just above the stomach). This may cause some discomfort in my nose, and there may be some gagging as I swallow the balloon.

7. I understand that trained personnel will be available at all times during testing so that any adverse reaction shall receive immediate attention. I also know that either IPPB or CN may be used if I am hospitalized regardless of the device which I am assigned for home use.

8. I understand that if my assigned treatment routine, with IPPB or CN, is determined to be less beneficial than another mode of treatment, I will be promptly notified.

9. I agree to allow my name and medical records to be made available only to physicians and research workers participating in the project.

10. I have been informed that I may withdraw from this study at any time, that I may receive IPPB or CN treatment without participating in this study, and that necessary medical treatment will not be denied to me solely because of a decision not to participate or withdraw from the study.

11. I have discussed the above information with my physician and he has answered my questions about my treatment program.

12. Some of the chemically and pharmacologically related drugs which have been investigated for treatment of patients with my disease have been found to produce benign tumors in rats when administrated in high doses.

13. Machine treatment with metaproterenol will not be continued for pregnant female patients because the effect of the drug on mother and child has not been determined.

D. Treatment Assignment

Each patient who has given informed consent for participating in the study and who has been judged eligible by a study physician will be randomly assigned to one of two treatment groups, IPPB therapy or compressor nebulizer therapy. The treatment allocation will be issued by the Data Center after the qualifying examinations have confirmed the patient's eligibility. Treatment assignments will be made using randomization schedules prepared separately for each clinic. These schedules will be prepared by the Data Center prior to the start of patient recruitment and will be designed to balance numbers of patients assigned to each of the treatment groups, throughout the period of recruitment.

The patient will be randomized into the study when (1) the Data Center has received and confirmed all data contained in Form 702, and (2) confirmation has been received by telephone that the Baseline Data has been completed with no change in eligibility. The clinical investigator or his delegate will telephone the Data Center between 8 a.m. and 5 p.m. EST, and give the Data Center the identifier number of the patient for which a treatment assignment is desired and confirm patient eligibility. The investigator will then be told whether the patient is in the IPPB group or the compressor nebulizer group. A letter confirming this treatment assignment will be mailed to the investigator soon after the verbal assignment. After randomization, a patient found to have been ineligible on the basis of information prior to randomization, should be excluded from the study. For all other cases randomization is irrevocable.

E. Reporting of Study Results

All data required by the Protocol will be forwarded to the Data Center for storage, processing, and statistical analysis. All data will be entered on the standard forms and forwarded to the Data Center within the time schedule outlined by the Data Summary Schedule Table.

The Data Center will periodically distribute formal reports to DLD and the clinics as outlined in Section VI. As described in Section VIII, 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, determination of the comparability of treatment groups at baseline, evaluation of the differences between treatment, and, to the extent possible, comparisons with literature controls or other patients with COPD.

F. Quality Control

The clinical and laboratory data will be collected and recorded on data forms by the personnel at participating centers. The pathology data will be recorded on data forms by the Central Pathology Center. All data forms will be mailed to the Data Center within the time schedule provided. The forms will be scrutinized and converted to machine readable form by the Data Center personnel. Procedures to ensure that the data are accurate, will be followed by the Clinical Centers, Pathology Center, and the Data Center.

Rigorous control for the data collection and recording will be maintained by the principal investigator at each center. It is realized that a variety of personnel will be required to enter data on the forms for the study. The principal investigator or his delegate at each center, however, will have the responsibility of scrutinizing each data form and giving final approval in the form of a signature. The Data Center will insist that all forms be reviewed by the principal investigator or his delegate and not a technician or medical secretary who may be involved with the project.

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 Center will review all data submitted to the center to ensure that it is free from errors and inconsistencies.

The data forms received from centers will be logged into a register. This register will show the type of form, patient identification number, and date of receipt; and correlate these dates with the schedule dates for data acquisition and forwarding. All forms will be edited by computer. The edit will focus on data completeness, internal consistency with previous data for the same patient, numerical values outside of specified limits, invalid codes, and the like. Errors detected in the editing process will be sent to the clinics for corrections. Follow-up procedures will be established to assure that all errors get corrected and returned to the Data Center. The data collected regarding completeness and accuracy of the information from the

Individual data forms will be summarized as percent correct and percent missing per form. These will serve as one basis for maintaining quality control at the participating clinic level.

G. Ancillary Studies

Ancillary research studies may be conducted by the clinical centers if approved by the Steering Committee, Program Office and the Advisory 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 treatment assignment or the subsequent therapeutic treatment regimen. The purpose of this interdiction is to assure a homogeneous application of the protocol to all patients.

H. Publicity

The advantages of efforts made by individual participants to make known to the medical community their involvement and interest in the collaborative program are recognized. Such efforts are, in fact, necessary and are strongly endorsed. However, publicity of information concerning the total program in the lay press can easily become distorted and may not reflect the general policies and opinions of all individuals involved in the study. Therefore, all inquiries concerning the total program must be referred to the DLD program office.

I. Publication and Presentations

The preparation and presentation of the results from the collaborative study to the biomedical community are the responsibilities of the participants and the Steering Committee.

The cumulative results from the total study will not be presented to the Steering Committee until the completion of the follow-up period or as directed by the DLD program officer. A final report, summarizing and analyzing the results from the total study, will be prepared. The preparation of this report will be the responsibility of the Steering Committee with supplemental assistence from the Data Center. This collaborative report, or a summary thereof, may be published for the biomedical community in an appropriate journal with a list of all principal investigators as participants. The Steering Committee and the DLD program office will develop guidelines for all other presentations and publications. It is understood that participation in the clinical trial constitutes a willingness to handle the presentation and publication of data from the study in a manner appropriate to the best interests of the total program as determined by the Steering Committee and DLD. The DLD program officer requires that credit be given to the IPPB Clinical Trial and a copy of all publications be forwarded to DLD.