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MANUAL OF PROCEDURES

Clinical Study of Intermittent Positive Pressure Breathing

Data Center for the IPPB Study
Biostatistics Center
George Washington University

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APPENDICES

I. Patient Eligibility, Evaluation, Treatment, and Followup

A. Criteria for eligibility

To be considered for this study, all patients must be 30 to 74 years of age, have chronic obstructive lung disease, meet all entry criteria listed below and have none of the exclusion criteria.

1. Entry Criteria

a. All patients must have symptomatic COPD (symptoms must include chronic cough, sputum production, or dyspnea).

b. All patients must satisfy the following pulmonary function measurements twice, not less than one week or more than 90 days apart, while on the standard regimen (Manual Section B1).

1) The prebronchodilator FEV_1 is less than 60% predicted and the prebronchodilator FEV_1/FVC ratio is less than 60%.

2) The prebronchodilator FEV_1 values must be reproducible, that is agree within 15% of the higher value or within 0.2 Liter.

c. All patients must have completed a 30 day stabilization phase on a standard regimen (see Appendix A).

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

1) Be ambulatory and able to sit on and pedal the bicycle ergometer.

2) Live close enough to the clinic to be accessible for home and clinic visits.

3) Demonstrate reliability during the stabilization period.

4) Provide informed consent.

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 150 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. Specific diseases for which a patient would be excluded are as follows:

   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 infarction within the last six months, or significant valvular heart disease.

   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 used either propranolol or cromolyn sodium during the 30 days of stabilization.

f. The patient used home IPPB or compressor nebulizer during the 30 days of stabilization, or used IPPB for more than 30 continuous days in the 6 months prior to identification. Patients who have used a compressor nebulizer during the past 6 months are eligible only if they can remain without it for the stabilization phase and agree not to use it if they are assigned an IPPB machine.

g. The patient used home oxygen supplementation (for 12 or more hours a day) during the 30 days of stabilization, or used such treatment for more than 30 continuous days in the 6 months prior to the start of stabilization, or the patient, on initial evaluation, meets the criteria for home oxygen administration listed in Appendix A.

bronchodilator administration).

B. Standard regimen and experimental treatment

1. All patients

The following standard regimen will be used during the 30 day stabilization period and throughout the course of the study. Further details are given in Appendix A.

a. Oral theophylline

All patients who can tolerate oral theophylline should receive a long-acting theophylline preparation. Serum theophylline concentrations will be measured to determine the dose required to achieve therapeutic levels. Patients who cannot tolerate any theophylline preparation, or who do not reach acceptable serum levels before experiencing side effects may be given oral beta-agonists.

b. Inhaled beta adrenergic agents

All patients will be supplied with freon-powered metered dose inhalers of metaproterenol. During the stabilization phase the inhaler should be used 2 whiffs qid.; during the study phase after baseline the inhaler will be used only when needed to supplement the bronchodilator delivered by IPPB or compressor nebulizer or in place of theophylline for intolerant patients.

c. Antibiotics

Antibiotics will be used for documented bacterial pulmonary parenchymal infections and presumed or proven bacterial bronchitis.

d. Corticosteroids

Chronic oral or inhaled corticosteroid treatment will be used only for patients who are found to have symptomatic and/or physiologic improvement demonstrated in a standardized therapeutic trial.

e. Other therapies

Diuretic agents, digitalis, oxygen supplementation, expectorants, bland aerosols, chest physiotherapy, postural drainage, and exercise training may be used as described in Appendix A.

f. Education

All patients will complete the educational program described in Appendix B.

2. IPPB Group

The IPPB device used for all study patients will be the Bennett AP-5 with the Bennett breathing circuit and nebulizer. Metaproterenol, diluted in sterile water, will be administered over a 10-15 minute period 3 or 4 times a day. The machine will be adjusted to deliver a tidal volume of at least 15 ml/kg body weight or at least 75% of the inspiratory capacity if 75% of the inspiratory capacity is less than 15 ml/kg. Detailed patient instructions are given in Appendix C.

3. Compressor nebulizer group

The Bennett compressor and the identical Bennett nebulizer used with the IPPB device will be used by these patients. Metaproterenol will be used in the same dose and dilution as for the IPPB group. 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 75% of the inspiratory capacity is less than 15 ml/kg. Detailed patient instructions are given in Appendix C.

C. Outline of patient evaluation and followup

The objectives of the study require the selection of a sufficient number of patients who meet the eligibility criteria. These patients will be put on a standard therapeutic regimen, be randomly assigned to one of the experimental treatments (IPPB or compressor nebulizer), and have their treatment supervised and clinical status observed during a three-year period of followup. More specifically, this will require the following steps:

1. Define an accessible group of potential study patients;
2. Screen all members of this group on selected eligibility criteria;
3. Place all patients selected by screening on a standard therapeutic regimen for a 30 day stabilization period;
4. During the stabilization period, determine whether the patient meets the additional eligibility requirements;
5. At the end of the stabilization period, record baseline characteristics for each eligible patient; these data are the starting point for measurement of change during experimental treatment and serve to classify patients into groups for which the effects of treatment may differ;
6. Assign individual eligible patients randomly to one of the two experimental treatment groups;
7. Instruct the patient in the assigned experimental treatment (see Appendix C), and initiate treatment;
8. Supervise treatment by means of scheduled periodic home and clinic visits, during which information is recorded on adherence to treatment regimen, clinical status, pulmonary function, exercise tolerance and blood gases, and indicators of quality of life;
9. Provide care for and record information on acute exacerbations of COPD and other illness;
10. Transmit data periodically from the cooperating clinics to the data center on standard data forms (see Appendix D) for entry into the master data file; for assessment of data quality and adherence to protocol provisions by the cooperating clinics; and for monitoring the progress of the study;

11. Analyze the relative effects of the two experimental treatments, periodically and at the end of the study, in terms of various outcome measures on which data have been recorded.

12. The types of data and the times at which they are to be recorded are summarized in Table 1. Manual Sections E through S of this chapter contain detailed instructions on the procedures to be followed and the data to be recorded at the clinic and home visits.

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)(KASR)	X		X		X				X				X
c. Profile of Mood Status (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
(4) Also when equipment culture positive

D. Preparation of standard data forms

All of the study data which the cooperating clinics forward to the data center will be recorded on standard forms (see Appendix D) that have been approved by the Steering Committee. This section provides information and instructions that are common to all or most of the standard forms.

Changes in the standard forms will be kept to a minimum. Any changes that are necessary will require approval by the Steering Committee and will be introduced simultaneously in all cooperating clinics.

1. Patient identification

Each clinic has been assigned a "treatment center number" as follows:

1. Houston
2. Loma Linda
3. Oklahoma City
4. San Francisco
5. Winnipeg

Each potential candidate for the study will be assigned a four digit identification number (0001, 0002, etc.) at the time information is entered on the Screening Log. The data center should never be sent the patient's name or social security number. For this reason, the patient's date of birth will be entered on each form for use in detecting errors in patient numbers. This information should be recorded in Section A of each form. The treatment center number, patient number, and date of form should also be recorded at the top of all pages after the first page in case the pages are accidentally separated.

2. Completion of forms

The following general instructions apply to all forms. Form 702 will be used as an example.

a. No-Yes questions

For this type of question two columns appear on the right margin of the form, labeled No and Yes, as in the following example.

	NO	YES	
G.2. Has the patient agreed to sign the informed consent?	[1]	[2]	263

For each question a ✓ should be placed in the appropriate box. (The small numbers within and to the right of the boxes are for data center use.)

b. Multiple choice questions

For multiple choice questions two or more answers exist, one and only one of which must be selected. In the following example a ✓ should be placed in the appropriate box.

D.2. Current employment status (check only one)	employed	[1]	71
	student	[2]	
	houseperson	[3]	
	retired	[4]	
	disabled	[5]	
	unemployed	[6]	

c. Numeric answers

For questions with numeric answers a series of boxes are provided, one for each digit.

F8. FEV_1 % predicted [ ][ ]

If the answer requires fewer digits than are provided for, zeroes should be used to fill the extra spaces to the left of the number, not the right. In the above example 9% would be recorded as 0 9. The number is said to be right justified. For dates, the month, the day, and the year are all right justified and the leading zero should be included. If the answer can have a fractional part then a decimal is provided, for example:

F7. FEV_1 (liters) [ ][.][ ][ ]

If a decimal is not provided, then the answer must not include a fractional part.

d. Rounding

If a number has more decimal places than the form provides, round upward if the extra digit is 5 or greater.

e. Skip Rules

In some forms entire sections should not be completed if they do not apply to the particular patient. For example, on Form 710 there is a question asking whether each procedure was performed. If it was, then all questions in that section should be answered. If not, then all questions should be left blank, as indicated by the "SKIP" statements on the form.

In other instances there may be only one question which may be left blank. For example, on Form 702:

		NO	YES
D3.	If the patient is retired or disabled was this due to lung disease?	1	2

This would be answered only if the categories 'disabled' or 'retired' were checked in the previous question (D2 above).

f. Missing data

If data are temporarily unavailable the item may be left blank (an error message will be sent and the answer should be recorded on it). If the data are permanently unavailable, enter 9's in <u>all</u> spaces.

g. Changing data

If you have to change a number cross it out and write above it. Do not write over the wrong number since it is usually difficult to tell the new value from the old.

The data forms developed for use in the study will not always exactly accomodate the data you are reporting. If the number of boxes, the definition of the data item or decimal point do not allow the data to be entered properly please attach a note to the front of the form stating the problem. The data center will see that it is coded correctly. The form should not be altered to accomodate data. This will cause many problems possibly including wrong data entered for a particular item that may never be discovered.

3. Review of completed forms

Each completed form should be reviewed for accuracy and completeness before the patient leaves the clinic. The form should be signed and dated by the individual who is responsible for the information on the form.

4. Transmittal to Data Center

Once each week the clinic will send completed forms to the data center (Form 701 will be sent every other week). The preferred mailing time is the institution's outgoing Friday mail, or earlier if that is necessary for the mail to get to the Postal Service, so that transit time is over the weekend. Regular first class mail will be used. Envelopes will be supplied by the data center for its convenience in sorting and processing mail.

All forms included in a weekly transmittal will be listed on the appropriate numbered and dated Weekly Batch Log (Form 750). This form provides a record of the treatment center number, form number, and patient ID number for each form. Forms will be sorted and listed in order of form number and patient number. One copy of the log will be included with the forms, a second copy mailed to the data center in a separate envelope, and a third retained in the clinic. If no forms are being sent in a particular week, the batch log should still be sent, indicating that zero forms will be sent.

5. Supplies of forms

The data center will send each clinic an initial supply of forms for use during the first year. Most of the forms will be printed on two-part, no carbon required paper, and the clinic will not have to make copies.

The clinic should maintain an inventory of all IPPB Study forms in stock. Additional copies should be ordered from the data center whenever there are fewer than 25 copies left.

E. Screening potentially eligible patients (Form 701)

1. Definition of potential candidates

A potential candidate for the study is a patient who:

a. is 30-74 years of age,

b. has symptomatic COPD,

c. has a prebronchodilator FEV_1 less than 60% predicted and a prebronchodilator FEV_1/FVC ratio less than 60%,

d. is ambulatory,

e. lives near enough to the medical center, and

f. is able to communicate in English.

2. Methods of finding potential candidates

At the beginning of the study each clinic shall provide the Steering Committee with a written description of its proposed methods of finding potential candidates for the study. All potential candidates, as defined above, who are found using this chosen method should be entered on the Screening Log. If more candidates are found than the clinic can evaluate, then the clinic should develop, with assistance from the data center, a systematic method of excluding some patients, such as screening only every other week.

3. Identification numbers

Each new patient will be assigned an identifying number (ID#), starting with 0001, at the time he is entered on the log. The patient's name should never appear on the copy of 701 sent to the data center. This will remain his study number if he is eligible and randomized. The patient's date of birth will also be used for identification in order to decrease the chance of errors in ID#'s.

4. Missing information

Columns 12-15, 16-21, 30, 31 and 42 (Patient ID, date of birth, source, sex, and submission of Form 702) must be completed for all patients who are potential candidates (as defined in Manual Section E1. above). Columns 32-41 should be filled with 9's if the data is unavailable. The FEV_1 data need not be from a recent spirogram.

Column 42 should never be blank on Form 701. If the information is incomplete, code a '2' and send Form 702 later. If you are unable to get any further information about the patient, cross him out entirely. If you don't know the exact FEV_1 percentages but are sure they are less than 60, put 99. If you think they are probably 60 or more, then remove the patient from the log.

5. Source of patient

Most patients will be found because of referral for symptoms of COPD (col. 30, code = 2), or through a review of FEV_1 values in a pulmonary function laboratory (code = 1).

6. Patients found to be ineligible when first evaluated

If, at first contact, a patient is found to be ineligible for the study (for example, because he is currently using IPPB at home, has cancer, or is not interested in the study), the reason(s) for ineligibility should be noted on the log using the appropriate code number(s) and no further information is required. If more than 4 reasons for ineligibility are found, then they should be chosen in numerical order except that numbers 26 and 27 should have first priority. At least one reason must be given if column 42 = 1. If less than 4 reasons are given, the remaining columns should be left blank.

If reason 36 (other) is used the reason should also be written of the log. Reason 36 should not be used if other reasons are given.

7. Patients who are not potential candidates

If patients are included who are not potential candidates, then the appropriate exclusion criteria should be recorded. For instance if a patient is unwilling to enter the study, but also does not have symptomatic COPD then both reasons 03 and 35 should be used. These patients will not be included in tabulations of the number of patients screened.

8. Patients who appear to be eligible when first evaluated

These patients should be started on a 30 day stabilization phase and eligibility data should be recorded on Form 702 (Initial Eligibility).

9. Transmittal of Form 701 to the Data Center

Form 701 should be copied (omitting names) and forwarded to the data center once every two weeks. A copy of Form 702 should be forwarded to the data center for every patient who

has not been classified as ineligible on Form 701 (for exception, see Manual Section E.10 below). Eight weeks after receipt of Form 701 the data center will contact the clinic for information on patients whose Form 702's have not yet been received.

10. Corrections to Form 701

If a patient is found to be ineligible after Form 701 has been submitted, but before he has his first eligibility spirogram, then a correction to column 42 of Form 701 (using Form 740) may be submitted instead of Form 702. One or more reasons for ineligibility must also be included.

F. Determination of eligibility (Form 702)

This form is to be completed for all patients who are not recorded as ineligible on Form 701. If Form 702 is inadvertantly forwarded to the data center for a patient who has not been listed on Form 701 or is classified as ineligible on 701, it will be rejected by the computer system.

It will take several clinic visits to investigate a patient's eligibility and parts of this form may be completed at each visit. If at any time the patient is found to be ineligible, the rest of the eligibility procedures and the rest of the form (other than Sections H and I) need not be completed. The initial or preliminary eligibility determination is based on the information in Form 702. Final determination of eligibility is based on Form 703, Pre-randomization Checklist, and the baseline data forms which must accompany it.

1. Preliminary entry criteria (section B)

   The patient must meet all the criteria in this section in order to be considered a potential candidate for the study.

2. Preliminary exclusion criteria (section C)

   Parts of this section may be completed at different times since some answers will be known when the patient is first seen and others will depend on the results of laboratory tests or other procedures.

   a. Questions 3-6 ask whether the patient will need home IPPB or compressor nebulizer, home oxygen therapy, propranolol or cromolyn sodium during the 30 day stabilization period. If any of these questions cannot be answered with reasonable certainty they may be left blank; the data center will then request the information at the time of randomization if the patient is not ineligible for other reasons.

   b. The chest radiograph, resting ECG, plethysmography, PaO_2, and hematocrit are needed both for eligibility determination and baseline. These procedures, and the creatinine level, may be postponed until baseline, in which case the relevant questions in section C should be left blank when Form 702 is submitted.

c. A chest radiograph, or resting ECG performed prior to the start of the 30 day stabilization phase may be used to determine eligibility. However, the procedures will need to be repeated at baseline if they were performed more than 90 days prior to randomization.

3. Background data (section D)

This section must be completed for all patients who appear to be eligible.

4. Stabilization phase and standard therapy (section E)

Each patient who appears to be eligible for the study is to be started on a 30 day stabilization phase during which he is to receive standard therapy (see Appendix A). The information that is to be recorded in this section is that which is prescribed as of the beginning of the stabilization period.

In the event of an acute illness during this time, the patient will be treated with appropriate therapy (see Appendix A).

5. Spirometry (section F)

Each patient must have spirograms (see Appendix G) on two occasions while on standard therapy (both before and after bronchodilator). The first must be obtained after the patient has been on standard therapy for at least 7 days. The second must be obtained at least 7 days but not more than 90 days after the first (See Manual Section J below).

In order for the patient to be eligible the prebronchodilator FEV_1 of both spirograms must be less than 60% predicted and the prebronchodilator FEV_1 /FVC ratio must be less than 60%. In addition the two FEV_1 values must agree within 15% of the higher value or 0.2 L. If at any time the FEV_1 or the FEV_1/FVC ratio is equal to or greater than 60% the patient is not eligible and additional spirograms should not be taken for study purposes. The second spirogram may be postponed until baseline, provided that the data meets the requirement of two spirograms no more than 90 days apart.

There is space on Form 702 to record spirograms obtained on from 1 to 4 separate days. The number of days should be recorded in item F4. Data from the first spirogram should be recorded in items F6-F14 under column #1. On each day FEV_1

and FVC will be measured at least 3 times before and after bronchodilator. Only the maximum of the 3 values will be recorded on Form 702. The maximum of the 3 prebronchodilator FEV_1 values should be recorded in item F7, the maximum of the 3 prebronchodilator FVC values in item F9, etc. These maximums do not all need to be from the same spirogram, but they must all be obtained on the same day. Data from the 2nd spirogram will be recorded under column #2. If spirograms are obtained on only 2 days and both are to be used for eligibility then items F20a = 1 and F20b = 2. If more spirograms are obtained, then the numbers of the two that are to be used for eligibility should be recorded in items F20a and F20b.

6. Quotas (section F)

The following quotas have been established to ensure the inclusion of patients with reversible obstruction and patients with both moderate and severe obstruction:

a. At least 20% of patients will show evidence, at least once, of reversibility (FEV_1 will increase at least 15% with acute bronchodilator administration).
b. At least 25%, but no more than 75%, of patients will have moderate airflow obstruction (prebronchodilator FEV_1 between 40% and 60% of predicted).

The data center will tabulate quarterly the number of patients in each quota. However, a clinic will stop randomizing patients in a category only after one of the following has occurred:

a. The number of patients without evidence of reversibility reaches 160.
b. The number of patients with FEV_1 between 40% and 60% of predicted reaches 150.
c. The number of patients with FEV_1 less than 40% of predicted reaches 150.

7. Reliability and informed consent (section G)

A judgment on the patient's reliability should take into account 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 evaluations.

The patient should sign a preliminary informed consent at the beginning of the stabilization phase and a final informed consent prior to the start of baseline studies.

8. Transmittal of Form 702 to the Data Center

Form 702 for ineligible patients should be forwarded as soon as the patient is found to be ineligible.

For patients who appear to be eligible, the form may be forwarded when the patient has had the second eligibility spirogram (first, if second is being postponed until baseline) and all other sections of the form have been completed. It is not necessary to wait until the end of the stabilization phase. A patient cannot be randomized before his Form 702 has been received and been reviewed by the data center.

9. Re-evaluation of ineligible patients

Patients who are found to be ineligible for reasons other than unreliability or illnesses that decrease life expectancy may be reconsidered as candidates for the study when 6 months have elapsed since the time of their original rejection.

These patients should be assigned the same ID# they had before. It is suggested that the clinics either put a note containing the ID#, date, and reason for rejection in the chart of each patient who is rejected, or keep a card file in alphabetical order of all patients assigned ID#'s.

G. Recording baseline data (Forms 703-705, 710-714, 730-733)

1. Purpose of baseline data

The pulmonary function (710), exercise (711), ECG (713), chest radiograph (714), and quality of life questionnaires (730-733) provide a base from which changes will be measured. These are all repeated during followup.

The data will also be used to classify patients for analytical purposes. Some examples are (1) patients with and without severe obstruction and (2) patients with and without emphysema.

In addition, the pulmonary function tests, ECG, and chest radiograph are necessary to confirm the patient's eligibility for the study.

2. Timing of baseline data

Baseline data cannot be obtained until after the end of the 30 day stabilization phase. The only exception is that an ECG or chest radiograph obtained either prior to or during the 30 day stabilization phase may be used as baseline if the patient is randomized within 90 days of the date these were obtained.

The patient must sign the final consent form prior to the start of the baseline studies.

All baseline data must be collected before randomization. Baseline data forms should not be sent to the data center before the patient has been randomized as they will be rejected by the computer system.

Ideally, baseline studies, randomization, and the initiation of the experimental therapy (IPPB or CN) should occur within a couple of weeks of the determination of patient eligibility. The following are <u>maximum</u> time intervals:

a. The baseline pulmonary function tests, symptom history, and physical exam should be otained within 3 weeks of randomization, and must be no more than 30 days before the start of IPPB or CN treatment.

b. IPPB or CN should be started within 2 weeks of randomization.

Each clinic should establish an order for the collection of baseline data. For each patient, Form 702 should be reviewed to determine if any required information was postponed until baseline. A schedule of tests should then be developed which will meet the time constraints listed above.

3. Repetition of spirometry

If baseline pulmonary function tests have been performed and any one of the following has occurred:

a. the baseline FEV_1 is not within 15% or 0.2 L. of one of the eligibility spirograms, or

b. the patient has not been randomized within 30 days of the baseline tests,

c. the patient has had an acute exacerbation after baseline, but before randomization,

then the spirometry portion of the baseline data should be repeated. The repeat spirogram should not be entered onto Form 710, but should be given to the data center by telephone at the time of randomization (to be added to Form 702). If the repeat FEV_1 does not agree with the baseline FEV_1 within 15% or 0.2 L., or if more than 60 days have elapsed since baseline, then all pulmonary function tests will have to be repeated.

4. Pre-randomization Checklist (Form 703)

This form should be used for final eligibility determination and as a control sheet for the completion of the other baseline forms.

a. The questions in sections B and C are designed to detect any changes in the patient's condition which would make him ineligible for the study. If a patient was reported as eligible on Form 702, but is later found to be ineligible, then Form 703 should be forwarded with the reason(s) for ineligibility summarized in section E. No other forms should be forwarded for ineligible patients.

b. Data for every form listed in section D must be collected before the data center is called for treatment assignment.

The assigned treatment should be recorded in section E. The form should be mailed to the data center within one week of randomization. The only data that may be missing are the KAS-R, the pressure volume curves, DLCO, or Phase II of exercise.

5. Baseline Symptom History, Physical Examination and Laboratory Data (Form 704)

The patient should be given the symptom history questionnaire (Appendix E). His answers should be recorded on Form 704.

6. Pulmonary History Questionnaire (Form 705)

The patient completes this form himself. He may do this at home or while waiting at the clinic. The form should be carefully checked for completeness after the patient has finished it. The occupations in section D should be coded by the clinic staff (see Appendix F for codes).

7. Pulmonary Function and Exercise Tests (Form 710, 711)

The details of pulmonary function measurements are described in Appendix G. All technicians shall receive formal workshop training before initiation of this study. Frequent on-site visits at each institution will be made to insure that the standard protocols are being followed.

As nearly as possible, all subjects will be tested under similar conditions. Oral and inhaled bronchodilators will be withheld at least 6 hours before testing starts. If patients forget or cannot tolerate this withholding period, the number of hours from the time the medication(s) was taken until spirometry (before bronchodilator challenge) begins will be recorded in questions C.4 and C.5, Form 710.

a. Testing Sequence

1) Step 1 - All of these tests must be done on the same day. The following sequence is recommended, but not required.

(a.) D_LCO

(b.) N_2 Washout, single breath (Slope, Phase III)

(c.) Plethysmography

(d.) Spirometry

(e.) Bronchodilator challenge

(f.) Wait 15 minutes

(g.) Plethysmography

(h.) Spirometry

2) Step 2 - These studies will usually be done on a different day than Step 1 but must be done within 5 days. If patients have fully recovered from Step 1, they may be accomplished the same day but individual patients should follow the same pattern for subsequent testing.

(a.) Lung mechanics

(b.) Exercise testing (includes arterial blood gases)

b. Specific data items - Form 710

The height and weight, questions D.1 and 2, may be recorded in centimeters or inches and kilograms or pounds (if only one is used the other should be left blank).

c. Specific data items - Form 711

Question C.2, "Skinfold thickness" will not be performed. This item may be left blank.

Question C.4, "Level completed" should match the last power output in which data is recorded (question C.5). For example if the highest power output containing data is 500 kpm then the level completed is 05. In addition, there must be an end point for phase I recorded (items C6 and D3).

In section E "Phase II", if data are not recorded for a particular exercise level (3 minutes or 5 minutes), 999 should be entered for the heart rate and the remainder of the column left blank. The 3 minute column should contain data for which the time collection started (E.3.k) is less than 3.5 minutes. Data collected 3.5 minutes or later should be recorded in the 5 minute column.

If phase II exercise is not performed, but the resting data is obtained, then question E1 should be answered yes and the power output should be recorded as 999 (E2). The heart rate for both 3 and 5 minutes should be 999.

8. Sputum and Equipment Evaluation (Form 712)

Equipment culture will not be obtained at baseline.

Sputum culture will be obtained only at baseline (and during illness). The patient should be instructed to obtain a sputum

specimen on a day in which he is coming to the clinic early in the morning. The specimen should be collected when the patient first awakens in the morning. Care should be taken not to collect specimens during meal time. The patient should be instructed to rinse his mouth with water (not a mouthwash), cough up material from deep in the lungs, and expectorate into a sterile wide mouth jar. (Saliva is not desirable.) When the sputum is produced, it should be expectorated immediately into the sputum container and not allowed to remain in the mouth while the patient catches his breath. The specimen should be labeled with the patient's name and the time the patient expectorated the specimen. The patient should bring the specimen (kept on ice) to the clinic within 2 hours. The culture coding system is described in Appendix H.

9. Interpretation of Resting ECG (Form 713)

   A standard ECG will be taken. Interpretation may be made by clinic staff and must be completed prior to randomization in order to supply information required for Forms 702 and 703.

10. Interpretation of Chest Radiograph (Form 714)

    Standard AP and lateral chest films will be taken. Interpretation must be sufficiently complete prior to randomization to supply information required for Forms 702 and 703. Detailed measurements, preferably done by a radiologist, for Form 714 may be postponed until later. (See Appendix I) For question C.7 "diaphragmatic shape", the most abnormal shape should be recorded.

11. SIP (Form 730), KASR (Form 731), POMS (Form 732) and RLCQ (Form 733)

    These forms should preferably be administered by someone other than the person who will be regularly visiting the patient's home. The interviewer might be one of the other nurses or a secretary. This person must have been trained in the administration of these questionnaires. The SIP, POMS and RLCQ are administered to the patient and the KAS-R to a relative or close friend. The patient and relative should not be together when these forms are administered.

The questionnaires should be administered in an environment that is reasonably free from noise and distractions. Good overhead lighting and a hard writing surface such as a desk or table should also be available. Before actually administering the questionnaires the interviewer should introduce himself to the patient or relative and attempt to put that person at ease. The interviewer should also explain the purpose of each instrument to the respondent, i.e., "this will help us learn about how treatment affects what people do, and how they think and feel".

The interviewer should encourage the respondent to complete all items, but should not use threats or other forms of coercion. In some cases it may be useful to appeal to the respondent's sense of altruism by noting that they will be helping to determine the best forms of treatment for persons like themselves.

a. The SIP should be administered by the interviewer. The interviewer should read the instructions to the patient from the separate instruction sheet (Appendix J) and then should read each statement exactly as it is written. Complete instructions are found in the SIP Interviewer Training Manual (Appendix K).

b. The KAS-R should be administered to a close relative (preferably spouse) or a close friend of the patient. This person should be sufficiently involved with the patient to be able to report on the patient's recent behavior in the home and have some knowledge of his outside activities. The same relative must be used at baseline and at 6, 12, 24 and 36 months of followup. The interviewer should read the instructions (Appendix L) before each section of the form. The questionnaire may be completed by the relative. However the interviewer should be readily available to answer questions and should check to see that all items have been answered. Some respondents with reading difficulties may need to have the questionnaire read to them. In this case, it is best to give the respondent a copy of the KAS-R to read along with the oral administration. The respondent may record his responses or, if necessary, the interviewer may do it for him.

c. The POMS should be completed by the patient himself. The interviewer should read the instructions as they are printed on the form. The patient should be shown how to mark the answers. No other instructions should be given. If the patient asks the meaning of a word he should be shown the dictionary definition. In most cases the interviewer need not remain with the patient. If the patient can not read the form or does not understand English well enough, then the test should not be administered. After the patient has finished, the interviewer should make sure that every item has been answered.

d. The RLCQ should be completed by the patient himself after reading the instructions that precede section B. The interviewer need not remain with the patient unless he has difficulty reading the form. After the patient has finished, the interviewer should make sure that every item has been answered.

Clinics that participate in neuropsychological testing should use Form 783 and the associated scoring instructions rather than Form 733. After the patient has completed Form 783 the interviewer will prepare Form 733, recording a "yes" for each item to which the patient checked "yes" for either 0-6 months or 7-12 months and a "no" for each item for which the patient checked "no" for both time periods.

H. Random assignment to the experimental treatment group.

Random assignment of treatment assures that the choice of treatment is not influenced by the patient's condition or any inadvertent or intentional biases. It also permits the application of statistical measures and tests for differences.

There is a separate computer-generated random sequence of treatments for each clinic. The computer has been programmed to create a balanced sequence in a manner that will not allow accurate prediction of any assignments.

Upon receipt of Form 702 the staff of the data center will check the eligibility criteria and will prepare a list of missing items. The spirometry related calculations will be verified. The clinic will be contacted if there are any discrepancies.

The clinic should call the data center when Form 703 has been completed and all baseline data has been collected, but no earlier than one week after the date that Form 702 was mailed to the data center. Randomization calls should be done once a week during which all patients for that week will be randomized. The clinic will then provide any missing eligibility data and confirm that all baseline data has been collected. If the clinic and the data center agree that the patient is eligible, the clinic will then be told the patient's treatment assignment. A written confirmation by the data center will follow. The clinic should record the assigned treatment and date of randomization on Form 703 and mail it to the data center within one week of randomization.

I. Initiation of experimental treatment (Form 706)

The assigned treatment will be initiated as soon as possible after the random assignment has been received by telephone from the data center (section H). This should be within three working days for most patients and must be within two weeks for every patient unless acute illness requires a longer delay.

The patient will receive instruction in the use of the equipment (Appendix C) and have a home demonstration of the use and care of his own machine. A determination that the facilities of the home are adequate and that any assistance needed by the patient in use and care of the machine is available should have been made during the establishment of eligibility. The machine will be checked for proper functioning during this home visit.

Form 706, Initial Machine Assignment, will be completed at the home demonstration visit. The initial tidal volume will be based on the patient's weight or on Inspiratory Capacity as recorded at baseline (Form 710, (Item H10). There are 5 spaces on the forms for recording the meter reading. The meters, however, have 6 numbers, the last of which is in red. A reading of 000015 is 1.5 hours. Record this on the form as 00015, dropping one zero from the left and ignoring the decimal.

The first two digits of the machine serial number should be 08 or 09 for IPPB machines and the first 3 digits should be 008 or 009 for CN machines.

J. Time Constraints

1. Definition of time constraints

The Protocol and Manual of Procedures set certain time constraints on procedures that must be carried out before a patient is started on one of the alternative treatments. These constraints are stated in terms such as:

a. Within, not more than (a maximum interval of time)

b. At least, after completion of (a minimum interval of time).

The latest acceptable date for a maximum interval and the earliest possible date for a minimum interval are defined to be the same date. That is, if a particular procedure was carried out on Friday, February 10, then Friday, February 17 is the latest acceptable date for a procedure that must be done within one week and is also the earliest acceptable date for a procedure that must be carried out at least one week later.

For 30 and 60 day intervals, the same rule about maximum and minimum intervals applies, but the method of determining the date must take into account the numbers of days in particular months. For 30 day intervals:

Month of beginning	Month of ending
30 day month	Same day of the month
31 day month	Same day of the month, minus one day
February	Same day in March, plus two days

For 90 day intervals, the appropriate combination of the above will be used.

2. Time constraints on procedures for entering patients (summary)

a. Eligibility spirograms:

(1) First spirogram must be done after at least one week on standard therapy.

(2) Second spirogram must be at least one week but not more than 90 days after the first.

(3) Second spirogram may be postponed until baseline.

b. Baseline data cannot be recorded until 30 day stabilization is completed.

c. The chest radiograph must be dated not more than 90 days prior to randomization.

d. The resting ECG must be dated not more than 90 days prior to randomization.

e. Exercise tests must be performed within 5 days of other pulmonary function tests.

f. All baseline data must have been collected before randomization.

g. Randomization must occur within 3 weeks of recording of certain baseline data (spirogram, symptom history, and physical exam).

h. Randomization must occur within 60 days of 2nd eligibility spirogram.

i. Treatment should start within 2 weeks of randomization, and must be started within 30 days of the date of baseline spirometry.

j. Patients who are found ineligible cannot be reconsidered for 6 months.

K. Followup visits: schedule of due dates

Upon receipt of Form 706 (Initial Machine Assignment), the data center will prepare for each patient a schedule of due dates for each monthly, quarterly, semiannual and annual visit. These due dates will be the same calendar days of the month without regard to weekends or holidays. Actual visit dates should be scheduled as closely as possible to these due dates. If there is advance knowledge that a patient will not be available for an extended period following a due date, the visit should be made early.

The due date for a visit will be the same day of the month that treatment was started, except that the due date for patients who start treatment on the 28th, 29th, 30th or 31st will be the 28th of each month. The schedule will also provide the starting and ending date for each of the 36 study months. Month 1 will start 15 days after the date therapy is started, with the following exceptions:

1. If the date treatment started plus 15 days is the 29th, 30th or 31st of the month, then month 1 will start on the 2nd of the next month.
2. If the date treatment started plus 15 days is the 1st of the month, then month 1 will start on the 2nd of the same month. Later months will start on the same day of the month as month 1.

APPOINTMENT SCHEDULE

CLINICAL CENTER: 4 PATIENT #: [redacted] DATE OF BIRTH: 10-02-20

IPPB TREATMENT STARTED ON: 10-25-78 DATE OF RANDOMIZATION: 10-23-78

STUDY MONTH #	STARTS	ENDS		HOME AND CLINIC VISITS NO EARLIER THAN	DUE DATE	NO LATER THAN
1	11-09-78	12-08-78	/	11-18-78	11-25-78	12-02-78
2	12-09-78	01-08-79	/	12-18-78	12-25-78	01-01-79
3	01-09-79	02-08-79	/	01-18-79	01-25-79	02-01-79
			/			
4	02-09-79	03-08-79	/	02-18-79	02-25-79	03-04-79
5	03-09-79	04-08-79	/	03-18-79	03-25-79	04-01-79
6	04-09-79	05-08-79	/	04-18-79	04-25-79	05-02-79
			/			
7	05-09-79	06-08-79	/	05-18-79	05-25-79	06-01-79
8	06-09-79	07-08-79	/	06-18-79	06-25-79	07-02-79
9	07-09-79	08-08-79	/	07-18-79	07-25-79	08-01-79
			/			
10	08-09-79	09-08-79	/	08-18-79	08-25-79	09-01-79
11	09-09-79	10-08-79	/	09-18-79	09-25-79	10-02-79
12	10-09-79	11-08-79	/	10-18-79	10-25-79	11-01-79
			/			
13	11-09-79	12-08-79	/	11-18-79	11-25-79	12-02-79
14	12-09-79	01-08-80	/	12-18-79	12-25-79	01-01-80
15	01-09-80	02-08-80	/	01-18-80	01-25-80	02-01-80
			/			
16	02-09-80	03-08-80	/	02-18-80	02-25-80	03-03-80
17	03-09-80	04-08-80	/	03-18-80	03-25-80	04-01-80
18	04-09-80	05-08-80	/	04-18-80	04-25-80	05-02-80
			/			
19	05-09-80	06-08-80	/	05-18-80	05-25-80	06-01-80
20	06-09-80	07-08-80	/	06-18-80	06-25-80	07-02-80
21	07-09-80	08-08-80	/	07-18-80	07-25-80	08-01-80
			/			
22	08-09-80	09-08-80	/	08-18-80	08-25-80	09-01-80
23	09-09-80	10-08-80	/	09-18-80	09-25-80	10-02-80
24	10-09-80	11-08-80	/	10-18-80	10-25-80	11-01-80
			/			
25	11-09-80	12-08-80	/	11-18-80	11-25-80	12-02-80
26	12-09-80	01-08-81	/	12-18-80	12-25-80	01-01-81
27	01-09-81	02-08-81	/	01-18-81	01-25-81	02-01-81
			/			
28	02-09-81	03-08-81	/	02-18-81	02-25-81	03-04-81
29	03-09-81	04-08-81	/	03-18-81	03-25-81	04-01-81
30	04-09-81	05-08-81	/	04-18-81	04-25-81	05-02-81
			/			
31	05-09-81	06-08-81	/	05-18-81	05-25-81	06-01-81
32	06-09-81	07-08-81	/	06-18-81	06-25-81	07-02-81
33	07-09-81	08-08-81	/	07-18-81	07-25-81	08-01-81
			/			
34	08-09-81	09-08-81	/	08-18-81	08-25-81	09-01-81
35	09-09-81	10-08-81	/	09-18-81	09-25-81	10-02-81
36	10-09-81	11-08-81	/	10-18-81	10-25-81	11-01-81

L. Home visits (Form 716)

Each patient will have monthly home visits for a period of 3 years, except every 3rd month when the home visit will be replaced by a visit to the clinic. Form 716 (Home Visit) will be forwarded to the data center but will not be keyed at the time it is received. Instead, the most important items from the home visit will be transcribed at the clinic onto Form 717 (Clinic Visit). Form 717 for month 3 will contain data from months 1 and 2, month 6 for months 4 and 5, etc. Alternatively, the home visitor may record information from the two home visits directly on the copy of Form 717 which is to be completed at the next clinic visit, and leave the corresponding items on Form 716 blank.

Weekly home visits are to be made during the first month to educate and assist the patient in complying with the treatment regimen. Form 716 may be prepared at these weekly visits for the clinic records but they will not be forwarded to the data center.

The following sequence is recommended for the home visit evaluation:

1. Physical Exam
2. Symptom History

   The patient should be given a copy of the written questionnaire to read (Appendix E) and his answers should be recorded in section C of Form 716.
3. Medical treatment evaluation
4. Compliance assessment

   The data in section G, Compliance with Treatment Regimens, in both Form 716 and 717 are the primary source of information on the extent to which the individual patient adheres to the treatment regimen. Plasma theophylline level provides a check on the adequacy of theophylline therapy but there is no corresponding confirmation with respect to machine therapy with metaproterenol. Thus, the data on prescribed dose of metaproterenol, prescribed amount of diluted solution, amount of solution used, and frequency and duration of treatments are of major importance.

The questions on number of theophylline pills taken, amount of diluted medication used, and number of days the machine was not used should cover the interval since the last completed visit, i.e., if a visit is missed, the numbers would be for a 2 month period. If it is impossible to give a reasonable estimate, record 9's instead.

5. Theophylline level blood sample

   A blood sample for theophylline determination must be drawn at home visits in the 5th, 17th and 29th month (section H). If that particular visit is missed or if the sample cannot be obtained, draw the sample at the next clinic or home visit, and record the data on the form for the visit at which it was drawn.

6. Machine culture with Aerotest

   Specimens for equipment culture will be collected at home visits in the 1st, 5th, 11th, 23rd and 35th months (section I). If that particular visit is missed or if the specimen is not obtained, collect it at the next home visit. The procedure to be followed is explained in Appendix M. The results of the culture should be recorded on Form 712 (see Appendix H). If the equipment culture is not done for a followup visit (month 1, 5, 11 etc.) code 999 for colony count, item D.1, and leave the rest of the section blank.

7. Machine performance evaluation.

   This should be done each month, but not before the machine culture in order to avoid contamination of the machine. Instructions are given in Appendix N.

8. Expired tidal volume measurement

   Instructions for performing this measurement at each home visit are given in Appendix O.

9. Machine replacement

   If the patient's machine has been replaced or run for more than an hour during servicing since the last home or clinic visit, Form 725 must be prepared (item F6, Form 716 or item G13, Form 717).

M. Clinic visits (Forms 710, 711, 713, 714, 715, 717, 730-733)

1. All clinic visits (Form 717)

The patient will have a clinic visit every 3rd month. Data from the two preceding home visits is to be recorded in section C of Form 717 (see Manual Section L above).

The sequence and instructions given in Manual Section L for Home Visits should also be followed during clinic visits.

During the clinic visit a judgment will be made as to whether the patient is in his usual state of health so that pulmonary function test values to be recorded on Form 715 (or 710) will not be substantially atypical (item F9, Form 717). If a judgment is made that the patient is having an acute exacerbation, Form 721 will be prepared instead of Form 715 and the patient will be asked to return for spirometry when he has recovered his usual state of health.

a. Treated exacerbation

If the patient has had a treated exacerbation since the last visit (item E2, Form 716), complete Form 720 if the patient was hospitalized or Form 727 if the patient was treated with antibiotics or steroids but not hospitalized.

b. "Off-schedule" patients

Occasionally a patient will become off schedule, due to missed appointments, illness, etc. This should be kept to a minimum; when this does occur attempts should be made to reschedule the patient as soon as possible.

Because of the differing forms, tests and information gathered at home and clinic visits the following general rules have been established for off-schedule patients. These rules will allow us to obtain the maximum useful information while keeping the patient on schedule, relative to baseline.

If a clinic visit is cancelled (i.e. month 3) and the patient cannot come in within one month (i.e. during month 4) then that clinic visit should be considered missed and the next clinic visit should be scheduled <u>early</u> in the next clinic visit month (i.e. first few days of month 6) in case a similar scheduling problem arises. Attempts should be made to complete the two intervening home visits (months 4 and 5).

In addition, if the annual clinic visit is missed (or months 3 and 6), where more extensive forms are required (i.e. quality of life forms), those forms should be "made up" at the following clinic visit. Thus, if month 3 visit is missed, at month 6 forms 710 (instead of 715) and 711 should be completed. However, if the patient is able to return in the intervening period, form 710 and 711 can be done then and, if possible, 715 done at month 6. Likewise, if month 6 is missed, forms 730-733 should be completed at month 9.

If the patient missed visit 3 clinic visit and <u>can</u> return during month 4 the clinic visit should be completed then and the two home visits (4 and 5) should be completed such that the next clinic visit (6) is on schedule. See page 32b for a flow chart for off-schedule patients.

Finally, it is very important that visits be completed sequentially. A month 4 home visit before a month 3 clinic visit causes many problems and should be avoided. If this situation should occur be sure to let us know so the data can be reported appropriately.

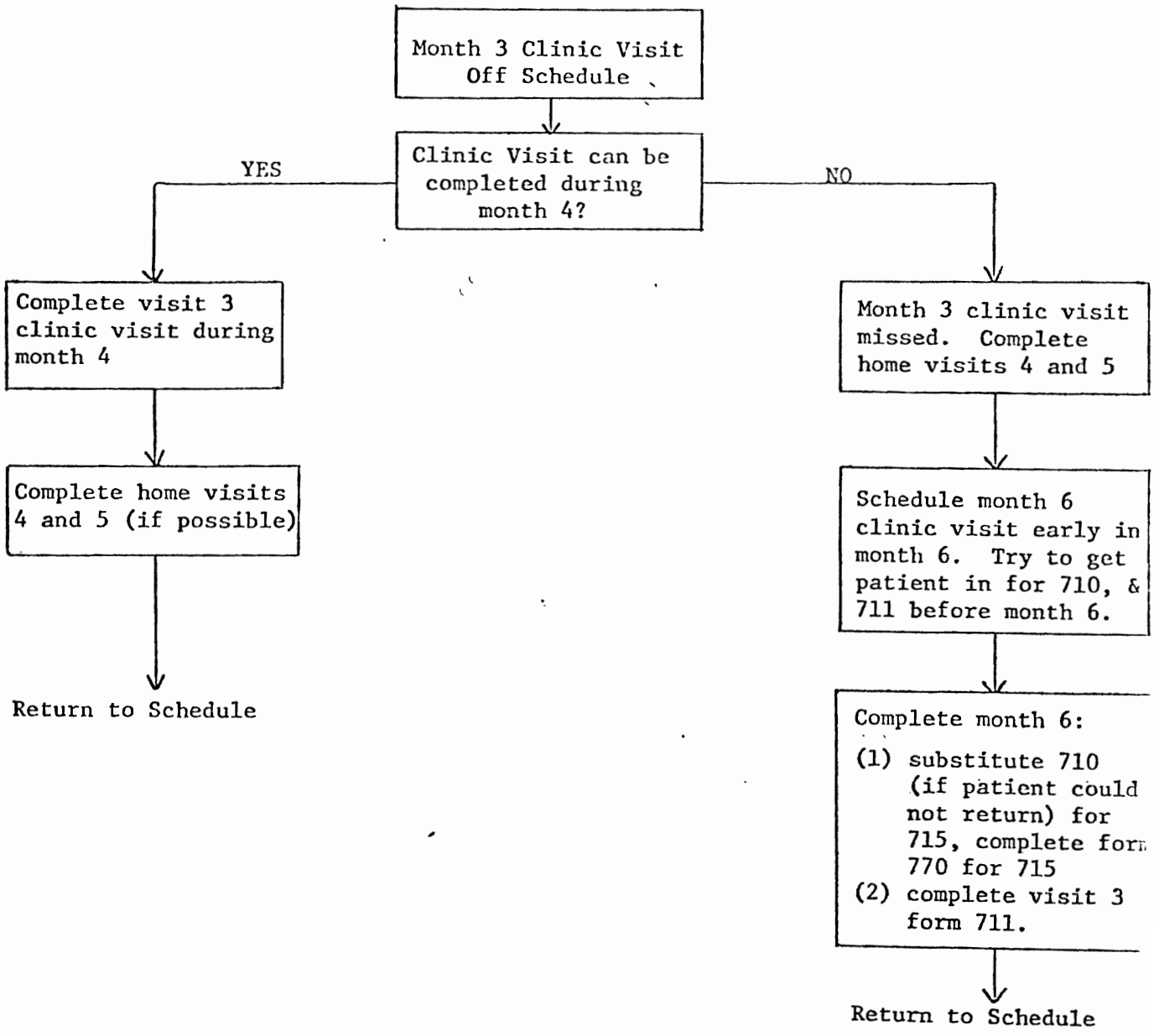
c. Missed visit

If the clinic visit is missed and the patient is not seen at home that month, then both Form 717 (Sections A-C only) and Form 724 (Missed Visit) should be completed.

d. Theophylline code list

Section H, question 16 of form 717 requires that the type of oral theophylline be coded. See Addendum Q for the appropriate code.

Flow Chart for Off Schedule Patients



d. Medication changes

All patients for whom Bronkosol was prescribed for machine use before metaproterenol became available for use in the United States in August 1978 have been changed over to metaproterenol. All patients entering the study after that date will start on metaproterenol. Patients who cannot tolerate metaproterenol may have Bronkosol (Barotec, in Canada) prescribed, but this change should be a clinical decision, made reluctantly, rather than a matter of patient preference. A memo should be sent to the data center giving the date and the reason for any patient whose medication is changed.

2. Semiannual clinic visits (Forms 715, 717, 730-732)

Forms to be completed at semiannual clinic visits are those completed at quarterly visits (Forms 715 and 717). In addition, three quality of life forms (Forms 730-732) are completed at month 6.

Instructions for these forms are given in the preceding Manual Sections G, L and M.

3. Annual clinic visits (Forms 710, 711, 713, 714, 717, 730-733)

All of the types of data recorded at baseline are repeated at the three annual clinic visits (months 12, 24 and 36) except for the pulmonary history and certain laboratory measurements. Every effort should be made to get every study patient to complete all parts of these major followup examinations, including those patients who are regarded as having dropped out of active treatment (Form 722 prepared) or who are otherwise non-compliant with the treatment regimen.

The data forms to be completed are 710, 711, 713, 714, 717 and 730-733. Instructions for these forms are given in Manual Sections G and M.

N. Followup pulmonary function tests (Form 710, 711 and 715)

Form 715 is to be completed at all quarterly clinic visits except those at 3, 12, 24 and 36 months, when complete pulmonary function studies are to be recorded on Forms 710 and 711.

The medication section on Form 710 (item C.2.a-o) need be answered only for the baseline (month 0) form. For followup visits this section may be left blank. All subsequent medication changes are recorded on Form 717.

Arterial blood gases are to be measured and recorded in section G of Form 715 at months 6, 18 and 30 only.

O. Other followup data (Forms 720, 723, 726 and 727)

Each of these forms provides followup data pertaining to outcomes of treatment. They are to be prepared whenever certain events occur, rather than on the basis of a schedule.

1. Form 720, Hospitalization.

Form 720 is prepared after discharge of a patient from an episode of hospital care. Thus, several forms may be prepared for a single patient during the three years of followup. If clinic staff are not actively involved in or are not aware that the patient has been in a hospital, item F2 of Form 717 provides a signal that Form 720 should be prepared.

2. Form 723, Death and Form 726, Pathology Report.

Form 723 and sections A-C of Form 726 are to be completed by clinic staff, and the rest of Form 726 is to be completed by the Pathology Center. Form 726 should be sent to the Pathology Center at the time the lungs are sent. Form 725 should also be completed (See Manual Section P4 below).

When a patient expires, a review of all the patient's data should be made to ensure that the data center has all the information required. If a home visit took place between the last clinic visit and the patient's death then a form 717 should be completed containing the home visit information with the clinic visit recorded as missed. For example if a patient dies after month 5 home visit then month 6 717 should be completed containing month 4 and 5 home visit information. It is not necessary, however, to fill out a form 724 for that "missed" clinic visit. Be sure to fill out form 770 for any missing forms due prior to the date of death.

Advance arrangements should be made with hospitals at which study patients are likely to seek care, in order that appropriate material be made available to the Pathology Center. Procedures to be followed are given in Appendix P.

3. Form 727, Non-hospitalized Acute Exacerbations

Form 727 is to be completed for each separate exacerbation that is treated with antibiotics or steroids. The form may be prepared during the exacerbation but should not be transmitted to the data center until after the patient has recovered because additional antibiotics or steroids may be prescribed (section C) and because hospitalization may be required. If the latter occurs, Form 720 rather than Form 727 should be prepared. Only one form should be prepared for each illness, even if several medications are prescribed.

If Septra is used the dose should be recorded as 400 mg.

P. Other Forms (Forms 721, 722, 724 and 725)

1. Form 721, Illness-related Spirometry

Form 721 will be prepared when a patient is in the clinic for quarterly, semiannual or annual followup but is suffering from an acute illness which makes his pulmonary function atypical of his usual state of health (see Manual Section M).

2. Form 722, Dropout

Form 722 will be completed when machine treatment with metaproterenol is to be or has been discontinued for more than 6 months for any of the reasons listed in section C of the form. Dropout may occur on the patient's initiative or on the basis of a clinical judgment that the patient is and will remain non-compliant with the treatment regimen for a period of six months or more.

After Form 722 has been completed, no further copies of Form 724, Missed Visit, need be prepared. Instead, an additional Form 722 will be prepared on the due date of each subsequent semi-annual visit until the end of the three year followup, the death of the patient, or his return to treatment and completion of a Form 717. The patient should be contacted at these six month intervals and attempts should be made to return the patient to the study. Final data (up until the dropout date) should be sent to the data center (see Manual Section I.0.2. on reporting final data for deaths).

3. Form 724, Missed Visit

Form 724 should be prepared for each clinic visit which is not made within the scheduled month and for which a home visit has not been substituted. The information contained in the form is important in that it reflects the patient's health status and reasons for missed visits.

Prompt preparation of Form 724 as soon as it is known that a visit will be or has been missed will not only result in better data but will avoid the preparation and response to an overdue visit message.

4. Form 725, Machine Replacement

Form 725 is to be completed when a patient has been given another machine to replace one taken back for servicing, repair

or discard. Form 716 (item F6) and Form 717 (items C10 and G13) provide reminders that Form 725 should have been prepared. If a patient dies or drops out a Form 725 should be completed with the last meter reading reported in section B and 9's written in for the new machine number in section C.

Q. Record keeping data forms (Forms 740 and 770)

1. Form 740, Data Correction Form

Form 740 is used to change data items on forms that have been previously sent to the data center. Corrections can also be made on edit messages (see Manual Section R) and Form 740 will be used for corrections other than those entered on edit messages.

2. Form 770, Notification of Permanently Missing Form

Form 770 is used to inform the data center that a regularly scheduled form that is due is permanently missing. Some of the situations making necessary Form 770 are: no relative for Form 731, patient refused to undergo testing, or a form was filled out but lost.

R. Edit procedures and error correction

1. Computer edit messages

A computer edit of incoming clinic data will be performed periodically at the data center. Errors such as missing values, out of range values, inconsistencies and skip rule violations will be printed out as edit messages. These will be sent to the clinic for confirmation and/or correction since the data center should not make any assumptions as to the correct values.

An example of a single-item edit message (missing or out of range) is given below. The clinic number, patient number, date of birth, and form number are printed at the top of the page, followed by a listing of the data on the form. All edits for that patient on that form will follow below the last broken line.

```
CLINIC 1    ID [redacted]    DOB 012226      FORM 7050    MONTH

EDIT              RUN 12 YEAR 1      22 JUNE, 1978
-------------------------------------------------------  ----------
0000000001111111111222222222233333333334444444445
1234567890123456789012345678901234567890123456789O  DISPLACEMENT
-------------------------------------------------------  ----------
7050031078[redacted]012226          211130122260502124            00
2121111111110103110032222252222222540605222224025 1            50
0000000000022251111 252112221112221222311221122 21             100
4    2000202  21      3000000001402144923000003000 0             150
000    21   0001      0           000   00         100           200
-------------------------------------------------------  ----------
0012   3333310100   21122                                      250
-------------------------------------------------------  ----------
0000000001111111111222222222233333333334444444445
1234567890123456789012345678901234567890123456789O  DISPLACEMENT
-------------------------------------------------------  ----------

C112-0016-7050-031078-[redacted]-012226-00-05155-8          <........>

              ITEM C2B COL   63  SEQ# 05155
              COUGH IN BAD WEATHER OTHERTIME   VALUE: 0
              MISSING VALUE
```

Numerical information (for the use of the data center) is printed out for each edit. This appears as a single line of numbers that contains the run number, edit number, form number, date of the form, patient number and date of birth, sequence number, and the value of the item after editing. The sequence number is a uniquely identifying number for an item on the computer's master file which does not appear on any of the printed forms. If an item is out of range or missing the value is replaced by 8's until a correction is received. Therefore, the value of the item will usually be 8 (or 88, etc.).

A description of the error is printed below the line of numerical data. This includes the item number, column number, sequence number, a brief description of the data item, the type of error, and the value on the form (blanks are keyed as 0 unless the symbol Ø is on the form, in which case the value will be blank). If the value is correct, then a ✓ should be made beside it. If it is incorrect, then the correct value should be written in the space above it (.....).

If there had been another single-item error on the same form, there would be another line of numeric data and description of the error.

The following example, also from Form 705, shows an edit message produced by a consistency check. In this case two lines of numeric data are printed, one for each of the items that might be in error. The values on the form are printed to the right of the lines of numeric data.

```
C101-0104-7050-010978-[redacted]-122227-00-05050-1        <.........> VAL: 1
C101-0105-7050-010978-[redacted]-122227-00-05420-1        <.........> VAL: 1

     ITEM B1  COL   30  SEQ# 05050          ITEM C27 COL  142  SEQ# 05420
     SEX                                   ARE YOU NOW PREGNANT?
     DOES NOT AGREE WITH
```

Below the lines of numeric data are descriptions of the two items that may be in error. The description on the left refers to the top line, the description on the right refers to the second line. In this example the patient is a male (col 30=1) and the question 'Are you now pregnant?' was answered "No" (col 142 = 1). If the patient is male, then col 142 should have been left blank. The correction should be made as follows:

```
.....          VAL : 1 √
..0...         VAL : 1
```

The check indicates that col 30 is correct and 0 is written in to change col 142 to blank. If the patient is a female who is not pregnant then the corrected error message would look as follows:

```
..2...         VAL : 1
.....          VAL : 1 √
```

Both items must be answered, either by writing in the correct answer or by putting a √ beside the value if it is correct.

Many edit messages for Form 702 will be in the form of consistency checks since data can be missing if the patient is ineligible, but not if he is eligible, as in this example:

```
C101-0023-7020-120877-[redacted]-122227-00-02840-2        <........> VAL: 2
C101-0024-7020-120877-[redacted]-122227-00-02417-0        <........> VAL: 0

        ITEM H1  COL  264  SEQ# 02840        ITEM E2D COL   85  SEQ# 0241
        ELIGIBLE FOR RANDOMIZATION          OTHER ORAL BRONCHODILATOR
        DOES NOT AGREE WITH
```

On Form 703 an error message will be produced if a patient is randomized but the 'wrong' answer is given to one of the eligibility questions.

```
C101-0065-7030-120888-[redacted]-122227-00-03310-2        <........> VAL: 2
C101-0066-7030-120888-[redacted]-122227-00-03260-1        <........> VAL: 1

        ITEM E1  COL   63  SEQ# 03310        ITEM D6  COL   56  SEQ# 03260
        PATIENT BEEN RANDOMIZED ?           QUALITY OF LIFE ?
        DOES NOT AGREE WITH
```

It should be noted that dates are coded as three separate fields and a missing date will result in three edit messages. A consistency check involving a date requires that 3 lines be printed since either the month, day or year might be wrong.

2. Computer update message logs

The purpose of the Update Message Log is to catch possible errors on forms by comparing them to information on other forms and patient schedules, via the header file. The header file is a set of data on each patient which is maintained on the master computer file, with which the corresponding data on each new form is checked in order to catch errors. These logs will be periodically sent to the clinics for comments and corrections. The different messages should be handled in 3 ways:

(a.) Those marked with a yellow marker should be looked up in the files and resolved. The answer should be recorded in the area for that message and copies of the log forwarded to the data center.

(b.) Those not marked by a yellow marker should be looked up in the files and, if correct, confirmed with a check (✓). These are mainly for informational purposes.

(c.) Those crossed out should be ignored. Either the problem has been resolved or the message was incorrect.

Copies containing the clinic's answers should be returned to the data center promptly; until discrepancies are fixed, more messages concerning the same items are likely to appear.

S. Other special procedures

1. Transfer of the patient to another clinic.

If a patient moves to an area where he can be followed by another clinic, and both the patient and the second clinic agree that he will be followed at the second clinic, then the patient will be considered a transfer. The first clinic should send a letter to the data center (and a copy to the second clinic) giving notification of the transfer and the effective date and the second clinic should send a letter to the data center stating acceptance of the transfer. The first clinic should send copies of all pertinent forms to the second clinic. The patient's identification number will not be changed and the first clinic's number will continue to be used. Edit messages will probably be sent to the first clinic and will have to be forwarded by them to the second clinic. The data center will report the patient's data with those of the first clinic. The transfer will be credited to the 2nd clinic in certain patient counts.

2. Ineligibility discovered after randomization.

A patient who is found to be ineligible on the basis of information that was available, but was not known, prior to randomization should be excluded from the study. The proposal to delete a patient from the study must be made by letter from the clinic or data center, and must be acknowledged by the other.

3. Temporary lapse of machine treatment

A patient who is unable to use his machine for a reason which is not permanent, (temporary illness or vacation, for example), should not be considered a dropout if he agrees to resume treatment when he is able. The number of days the machine was not used, the average number of uses per day and the prescribed medication should be recorded on Forms 716 and 717. Other questions on machine usage should be either left blank or filled with 9's as appropriate.

4. Supplemental oxygen at home

In order to have oxygen at home patients must have a PaO_2 of less than 55 mmHg measured twice, at least 2 weeks apart, while clinically stable and 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. The average number of hours per day and the average flow should be recorded on Form 717. Blood gases and exercise should be done both on room air and oxygen (Form 711 and 715). The patient should be off oxygen for at least 2 hours before the room air blood gases are performed. Phase I exercise should be done both on and off oxygen if possible. Phase II should not be performed.

T. Changes in Manual of Procedures and data forms

Clarifications and changes in the Manual are made by temporary memoranda from the data center to all clinics. Those that involve substantial change are reviewed with the Program Officer and the Chairman or the entire Steering Committee prior to issuance. Periodically a major revision of the Manual is made, incorporating and making obsolete the temporary memoranda.

Changes are also made in data forms as necessary to add, delete or alter items of data as indicated by experience. New versions of forms are transmitted to the clinics with memoranda pointing out the changes. Forms with minor changes carry a new date in the upper right corner; those with major changes involving substantial reorganization of the computer master file of data (version change) also carry a new decimal digit in the form number, from .0 to .1 etc.

Form changes are kept to a necessary minimum. In most instances a change in a form means that data submitted on earlier versions cannot be converted precisely to the full detail shown on the new version. All forms changes require extra work at the data center to achieve the best possible approximation to the data in the new version.

II. Data Management and Analysis

A. Outline of Data Center processes

When the weekly clinic batches are received by the data center the procedures below are followed.

1. The date is stamped on every form and document received.
2. The clinic batch logs are compared with the actual forms received and the forms are logged on the APL computer terminal. A program checks the following:
   a. Date of birth
   b. Form order: 702 and 703 before any other forms; 706 before any followup forms
   c. Correct month number (717 for months 3,6,9,12, etc., for example)
   d. Duplicate forms

   Any form not meeting these checks is removed and put in a separate file for correction.
3. Form 702 for eligible patients is separated from the batches and will not be keyed until after the patient has been randomized.
4. The date of randomization and treatment assignment on Form 703 are compared with the Randomization Log. If there are any discrepancies the clinic is called, as soon as possible, and these forms are processed as soon as corrections are made.
5. The remaining forms are combined from all clinics and put in one or more "data center batches" in order of form number. All corrections from previously edited forms are put in a separate batch.
6. A data center Batch Log, which records every form processed in the batch, is compiled and a covering "Batch sheet" is filled out. Totals of each type of form for each clinic are recorded (after recounting) and the forms are ready for keypunching.
7. The batch is keyed onto a magnetic diskette and verified, returned to the IPPB files, and placed in a folder marked "data in edit process."

8. The keyed data is transmitted to magnetic tape and edited for possible errors. The edits include checks for missing values, range checks, and consistency checks between items on the form. Calculated variables (TLC, predicted values, number of days between dates, scores for quality of life, etc.) are computed at this time. The edit program provides a count of the number of single item and consistency errors for each type of form for each clinic.
9. Edit messages are printed out on 2-part (carbon) paper. After checking for incorrect messages one copy is sent to the clinic for correction and a copy is retained at the data center in files marked "Outstanding Edit Messages" (by clinic). When the clinic returns a corrected message, the correction is keyed and transmitted to the Master File. The corrected message is filed in the subject's folder and the duplicate is discarded. A close watch is kept on all edit messages.
10. Any form 706 (Machine Assignment) that is processed will initiate the production of an appointment schedule. The appointment schedule is compared with the Randomization Log and is mailed to the clinic.
11. The Update program checks the edited forms (see 2 above) and, if acceptable, adds them to the patient's record on the master file. The Update program does not provide for editing between forms. However, certain items, such as height, machine number, and meter reading, are kept on a separate Header File so that these items on new forms can be compared to their values on previous forms. Any discrepancies are printed on the Update Message Log. Time intervals between baseline forms and randomization and between followup forms and their dates are also checked and any discrepancies are printed in the Update Message Log.
12. The Update program also makes corrections to the forms as specified in the correction records. Each corrected item on the master file is re-edited for missing and out of range values, the update checks are performed again, and the calculated variables are recalculated.

13. Forms rejected by the Update program are removed from the batch. These will be checked either with other forms in the files or by telephone with the clinics and, after correction, will be keyed with the next batch or filed without keying, depending on the problem. A log is maintained for all rejected forms.
14. After editing, the batch is disassembled. Forms are filed in individual folders for each ID and put in the appropriate clinic's file.

B. Control on receipt and location of data forms

As mentioned in Manual Section I.D.4, the clinics will send weekly batches to the data center. It is important that the pre-numbered batch sheet corresponds to the correct date of mailing. The clinic should maintain a current file of all batch listings so that they can easily determine when and in which batch each form is mailed.

The clinic should maintain a separate listing for each patient that shows which forms are due at each visit and whether or not they were sent to the data center.

The data center keeps the clinic's batch listings for checking purposes. Each form received in the weekly batch is entered onto a computer log (except Form 701) and a file is maintained for each ID that indicates which forms have been received by the data center.

At monthly intervals, several listings are produced and sent to each clinic which indicate overdue or missing forms. These include:

1. List of Overdue 702 Forms. This list includes the patient numbers for all patients reported eligible on Form 701 eight or more weeks prior and for whom a 702 has not been received by the data center.
2. List of Overdue Baseline Forms. This lists, for all patients randomized 45 days prior, the baseline forms that have not been received. A form will not be included if Form 770, Notification of Permanently Missing Form, has been received for that form.
3. List of Overdue Followup Forms. This lists followup forms of patients for whom neither forms nor Form 770 have been received within 45 days of the end of the scheduled month of followup.

C. Monthly reports on patient acquisition and data forms

The monthly report summarizes the forms received at the data center. The data center processes data once a week, usually the week after it is received. The decision to include forms in the monthly report will be based on the weekly run number rather than the date of the form. The monthly report will be prepared at the end of the week after the end of the month. The report will include either 4 or 5 weeks of data.

1. Tables 1 and 2 (Number of patients randomized this month and cumulatively)

   Form 702 will be used to count the number of randomized patients. Treatment assignment is on Form 702, but the date of assignment is not. Therefore, the run numbers of Form 702 will be used to determine the patients randomized during the month. This will provide an accurate count except when the month ends on a Thursday or Friday, in which case patients randomized on those two days will not be included, or when the patient's date of birth does not agree with the date of birth on Form 701 and his Form 702 cannot be entered into the computer file. For these reasons, the number of patients in Tables 1 and 2 will occasionally differ from the number of patients on the graph (this is based on the actual date of randomization).

2. Table 3 (Number of 702's for eligible patients)

   This table will be done by hand and typed.

3. Table 4 (Number of patients screened)

   This table counts the number of Form 701's added to the file in the run numbers for the month. Patients with incomplete data will be counted as eligible.

4. Table 5 (Reasons for ineligibility Form 701)

   This table shows the reasons for ineligibility for patients ineligible in Table 4. Patients may be ineligible for more than one reason. In most cases, each reason is counted, except

that the following reasons (as listed on Form 701) count as one reason:

28, 29	(Response to bronchodilator)
7, 9	(Home IPPB or CN)
8, 10	(Home oxygen)
13, 16, 20, 21	(Cardiac disease)

Reason 35 (Patient consent) is counted only if it is the only reason given or if it is given with reason 36 (Other) and no other reasons, in which case both reasons are counted. This is because the other reason often relates to the patient's unwillingness to participate in the study.

5. Table 6 (Reason for ineligibility on Forms 702 and 703)

   This table includes patients who were found ineligible on either Form 702 or Form 703. The reasons are the same as in Table 5 except that ineligibility on the basis of prebronchodilator FEV_1 has been added. On Form 701, these patients would not have been counted as candidates for the study. The assumption is that they improved with standard therapy.

6. Table 7 (Forms processed at the data center)

   This includes all forms added to the master file during the month.

7. Table 8 (Number of error messages per form)

   This table counts the number of single item errors (missing or out of range) and consistency errors for each form edited during the month.

8. Table 9 (Latest followup visit)

   This table shows the latest followup visit for each patient.

9. Table 10 (Number of overdue baseline forms)

   This table counts the number of missing baseline forms for patients randomized more than 45 days before this report. Form 703 is counted as missing if Form 702 was entered onto the file before the month of the report. Patients randomized before May 1, 1978 do not need to have Form 733.

10. Table 11 (Number of overdue followup forms)

    Table 11 provides a count of the number of overdue followup forms. A form is counted as overdue if it is not received within

45 days of the end of scheduled month. Form 733 is not required at month 0 for patients who started therapy before May 1, 1978. Form 712 is not required for patients who started therapy before January 1, 1979. Form 731 is not required for patients who did not have a baseline Form 731.

11. Table 12 (Number of missed visits)

This table reports the number of missing home and clinic visits, expressed as a percentage of scheduled visits. A visit is counted as missed only after Form 717 has been received.

APPENDICES

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 hours 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, 2 whiffs qid., and during the study phase it will be used 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 antibotics, 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 contradictions. 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. 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.

3. 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 breath 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 nursing 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).

APPENDIX B

Patient Education

Each patient will be taught basic COPD self care and how to use and care for his or her treatment machine according to study protocol. The teaching can be conducted in a manner appropriate to each Center as long as the content is consistent.

The components of the basic COPD education include (per Chicago Lung Association):

- Simple respiratory anatomy and physiology
- Brief description of COPD and its complications
- Treatment of COPD
- Therapeutic breathing techniques
- Bronchial hygiene
- Exercise program and home walking program

The components of the machine instruction include:

- Preparation and storage of medication
- Treatment technique
- Cleaning of tubing and manifold
- Care of machine

Educational Materials:

Chronic Obstructive Pulmonary Disease - A Guide for Teaching Patients, Chicago Lung Association, Chicago, Illinois, 1977 (change machine instruction according to study protocol)

IPPB, CN and metered-dose inhaler patient instruction sheets (Appendix C)

The Do's and Don'ts of Walking, Breon, Laboratories Inc., New York, 12/76

Optional instruction guides:

- Respiratory Rehabilitation - Breath Training
- Initial Conditioning Exercises for Trunk and Extremities
- Home Walking Program - Patient copy, nurse instruction sheet
- Home Program for Bronchial Drainage

Home Visit Activities:

Home visits will be made by the nurse or respiratory therapist for assessment, compliance and patient teaching once a week for the first month except for the week of the clinic visit and monthly thereafter for the duration of the study except for the month of the clinic visit.

The activities of the visit are described in the Study Protocol and Manuals of Operations as outlined below.

Week 1: -Clarify home visit sequence and activities with patient.
-Ask patient if he or she has any questions about the home visit.
-Review the administration and purpose of oral and inhaled medications. (A medication sheet may be given to each patient in the clinic outlining the medication schedule).
-Read elapsed machine time meter, note appearance of tubing and manifold.
-Review preparation and storage of machine medication, treatment technique and cleaning of tubing and manifold.
-Have patient demonstrate procedure.
-Measure machine delivered tidal volume and instruct patient to breathe to prescribed volume.
-Do pill count.

Week 2: -Ask patient if he or she has any questions about the machine or medications.
-Read elapsed machine time meter, measure machine TV, note appearnce of tubing and manifold.
-Observe patient preparing machine medication, taking treatment and cleaning manifold and tubing. Reinforce treatment technique and cleaning instructions if indicated.
-Reinforce or initiate basic COPD education according to study protocol.
-Do pill count.

Week 3: - Read machine elapsed time meter.
- Measure machine TV - reinforce breathing technique if indicated.
- Note appearance of tubing and manifold.
- Ask patient to describe medication preparation, treatment routine and care of manifold tubing.
- Continue or reinforce basic COPD education.
- Do pill count.

Monthly home visit (There will not be a home visit the month of the quarterly clinic visit.):
- Complete symptomatic and physical assessment on Form 716.
- Draw venous blood for plasma theophylline level, months 5, 17, 29.
- Read machine elapsed time meter.
- Obtain machine effluent culture months 1, 11, 23 and 35.
- Note appearance of tubing and manifold.
- Measure machine TV and reinforce patient breathing technique as indicated.
- Ask patient if he or she is having any problems with treatment and care of machine tubing, or manifold.
- Do pill count.
- Reinforce or initiate teaching and/or therapies according to study protocol and the direction of the physician and/or Principal Investigator.
- Notify M.D. and/or Principal Investigator or any unusual signs or symptoms and compliance problems.

APPENDIX C

IPPB TREATMENTS

TAKING YOUR TREATMENT

YOUR MACHINE IS CALLED A BENNETT AP-5 IPPB MACHINE.

TAKE TREATMENTS 3 to 4 TIMES DAILY, AT LEAST 4 HOURS APART.

PROCEDURE:

1. PREPARE _____
   _____
2. ADD MEDICATION TO NEBULIZER.
3. SIT IN COMFORTABLE POSITION WITH FEET FLAT ON FLOOR AND ARMS SUPPORTED.
4. TURN ON MACHINE. CHECK TO SEE IF IT IS NEBULIZING PROPERLY.
5. INHALE SLOWLY AND DEEPLY THROUGH NEBULIZER MOUTHPIECE. HOLD BREATH MOMENTARILY. EXHALE SLOWLY AND COMPLETELY THROUGH MOUTHPIECE.
6. REPEAT SLOW DEEP INHALATIONS UNTIL ALL MEDICINE IS GONE.
7. TAKE THREE DEEP BREATHS, USING PURSED LIP BREATHING TECHNIQUE.
8. COUGH DEEPLY THREE TIMES TO CLEAR SPUTUM FROM CHEST, KEEPING MOUTH OPEN. LEAN FORWARD AS YOU COUGH.
9. RINSE MANIFOLD AND MOUTHPIECE IN HOT RUNNING WATER AFTER TREATMENT - ALLOW TO DRAIN ON TOWEL UNTIL DRY.
10. BEGIN POSTURAL DRAINAGE, PERCUSSION AND VIBRATION IF IT IS NEEDED.

PROCEDURE FOR USE OF METERED-DOSE INHALER

1. HOLD NEBULIZER MOUTHPIECE IN FRONT OF WIDE OPEN MOUTH.
2. SQUEEZE NEBULIZER BRISKLY AS YOU INHALE DEEPLY THROUGH OPEN MOUTH.
3. HOLD BREATH 1 or 2 SECONDS TO ALLOW MEDICATION PARTICLES TO SETTLE IN YOUR LUNGS.
4. EXHALE THROUGH PURSED LIPS.

REPEAT ABOVE PROCEDURE IF YOUR PHYSICIAN ADVISES MORE THAN 1 PUFF AT A TIME.

NOTIFY YOUR PHYSICIAN IF YOU FEEL THE NEED TO USE YOUR NEBULIZER MORE OFTEN THAN EVERY 2 HOURS.

WHENEVER NECESSARY SEPARATE THE MOUTHPIECE FROM THE CARTRIDGE, WASH IT IN SOAPY WATER, AND RINSE IN HOT WATER. ALLOW IT TO DRAIN DRY ON A TOWEL.

COMPRESSOR NEBULIZER TREATMENTS

TAKING YOUR TREATMENT

YOUR MACHINE IS A COMPRESSOR NEBULIZER.

TAKE TREATMENTS 3 to 4 TIMES DAILY, AT LEAST 4 HOURS APART

PROCEDURE:

1. PREPARE_____

   _____

2. ADD MEDICATION TO NEBULIZER.
3. SIT IN COMFORTABLE POSITION WITH FEET FLAT ON FLOOR AND ARMS SUPPORTED.
4. TURN ON MACHINE. CHECK TO SEE IF IT IS NEBULIZING PROPERLY.
5. INHALE SLOWLY AND DEEPLY THROUGH NEBULIZER MOUTHPIECE. HOLD BREATH MOMENTARILY. EXHALE SLOWLY AND COMPLETELY THROUGH MOUTHPIECE.
6. REPEAT SLOW DEEP INHALTIONS UNTIL ALL MEDICINE IS GONE.
7. TAKE THREE DEEP BREATHS, USING PURSED LIP BREATHING TECHNIQUE.
8. COUGH DEEPLY THREE TIMES TO CLEAR SPUTUM FROM CHEST, KEEPING MOUTH OPEN. LEAN FORWARD AS YOU COUGH.
9. RINSE MANIFOLD AND MOUTHPIECE IN HOT RUNNING WATER AFTER TREATMENT, BE CAREFUL NOT TO GET WATER INSIDE THE EXHALATION DIAPHRAGM. ALLOW TO DRAIN ON TOWEL UNTIL DRY.
10. BEGIN POSTURAL DRAINAGE, PERCUSSION AND VIBRATION IF IT IS NEEDED.

CLEANING YOUR COMPRESSOR NEBULIZER

TWO TIMES EACH WEEK:

1. SEPARATE MANIFOLD PARTS. PLACE THE CAP ON THE EXHALATION DIAPHRAGM. (TUBING DOES NOT HAVE TO BE CLEANED UNLESS IT IS DIRTY)
2. SCRUB MOUTHPIECE AND MANIFOLD PARTS IN WARM SOAPY WATER (USE LIQUID DETERGENT.)
3. RINSE IN HOT WATER.
4. SOAK ALL PARTS IN SOLUTION OF 1 PART WHITE DISTILLED VINEGAR AND 2 PARTS WATER FOR 30 MINUTES
5. RINSE IN HOT WATER.
6. ALLOW TO DRAIN ON TOWEL. DO NOT WIPE DRY.

IF YOU HAVE TO WASH THE TUBING, SHAKE IT WELL AND HANG IT TO DRY OVER A TOWEL RACK OR SHOWER ROD. YOU CAN ATTACH THE TUBING TO THE AIR OUTLET ON THE MACHINE TO REMOVE WATER BUBBLES.

PROCEDURE FOR USE OF METERED-DOSE INHALER

1. EXHALE FULLY THROUGH PURSED LIPS.
2. HOLD NEBULIZER MOUTHPIECE IN FRONT OF WIDE OPEN MOUTH.
3. SQUEEZE NEBULIZER BRISKLY AS YOU INHALE DEEPLY THROUGH OPEN MOUTH.
4. HOLD BREATH 1 or 2 SECONDS TO ALLOW MEDICATION PARTICLES TO SETTLE IN YOUR LUNGS.
5. EXHALE THROUGH PURSED LIPS.

REPEAT ABOVE PROCEDURE IF YOUR PHYSICIAN ADVISES MORE THAN 1 PUFF AT A TIME.

NOTIFY YOUR PHYSICIAN IF YOU FEEL THE NEED TO USE YOUR NEBULIZER MORE OFTEN THAN EVERY 2 HOURS.

WHENEVER NECESSARY SEPARATE THE MOUTHPIECE FROM THE CARTRIDGE, WASH IT IN SOAPY WATER, AND RINSE IN HOT WATER. ALLOW IT TO DRAIN DRY ON A TOWEL.

APPENDIX D

List of Standard Data Forms

Clinical Study of IPPB

701 Screening Log
702 Initial Eligibility
703 Pre-randomization Checklist
704 Baseline Symptom History, Physical Examination and Laboratory Data
705 Pulmonary History Questionnaire
706 Initial Machine Assignment
710 Pulmonary Function Tests
711 Exercise Tests
712 Sputum and Equipment Evaluation
713 Interpretation of Resting ECG
714 Interpretation of Chest Radiograph
715 Quarterly Pulmonary Function Tests
716 Home Visit
717 Clinic Visit
720 Hospitalization
721 Illness-related Spirometry
722 Dropout
723 Death
724 Missed Visit
725 Machine Replacement
726 Pathology Report
727 Non-hospitalized Acute Exacerbation
730 Sickness Impact Profile (SIP)
731 Katz Adjustment Scale (relative's form)
732 Profile of Mood States (POMS)
733 Recent Life Changes Questionnaire (RLCQ)
740 Data Correction Form
750 Weekly Batch Log
770 Notification of Permanently Missing Form
783 Recent Life Changes Questionnaire (for Neuropsychology Study)

APPENDIX E

CLINICAL STUDY OF IPPB - SYMPTOM HISTORY - FORMS 704 and 717

Cough:

a. None - I do not have a cough.

b. Mild - I cough only in the morning and have little difficulty with coughing during the day.

c. Moderate - I cough in the morning with episodes of coughing during the day requiring rest and interfering with daily activities.

d. Severe - I cough throughout the day as well as at night. Coughing may cause me to have chest pain, dizziness, or unsteadiness.

Sputum:

a. None - I do not produce sputum.

b. Mild - I produce sputum mostly in the morning usually less than ¼ cup.

c. Moderate - I produce sputum throughout the day and it is usually ¼ to ½ cup per day.

d. Severe - I produce sputum throughout the day greater than ½ cup per day.

Shortness of Breath:

a. None - I have no restriction of normal activities.

b. Mild - I have shortness of breath when walking stairs or on an incline, but not on level ground.

c. Moderate - I get short of breath with routine daily activities and minimal exertion.

d. Severe - I am short of breath at rest as well as with any activity.

Wheezing

a. None - I never wheeze.

b. Mild - I have no wheezing at rest, but I occasionally wheeze with moderate exercise.

c. Moderate - I wheeze with most daily activities and with minimal exercise.

d. Severe - I wheeze at rest.

Fluid Retention

a. None - My ankles never swell.

b. Mild - My ankles swell after I stand or sit for a long time.

c. Moderate - My ankles swell when I stand or sit and get worse as the day goes on. The swelling goes away at night.

d. Severe - My ankles get more swollen as the day goes by, and the swelling usually does not completely go away at night.

APPENDIX F

Clinical Study of IPPB--Code for Occupations, Form 705.1

01 Professional and technical workers
Accountants
Architects
Computer specialists
Engineers
Lawyers, judges
Librarians
Physicians, dentists
Registered nurses, dietitians, therapists
Religious workers
Scientists (life, physical, social)
Social and recreational workers
Teachers
Technicians, technologists
Writers, artists, entertainers

02 Managers and administrators (except farm)
Buyers, purchasing agents, sales managers
Managers, administrators
Restaurant, bar managers

03 Sales workers
Agents, brokers (insurance, real estate)
Demonstrators, hucksters, peddlers
Sales clerks, representatives
Salesmen

04 Clerical workers
Bank tellers, cashiers
Bookkeepers
Clerks (billing, counter, file, mail, payroll, postal, time)
Enumerators, interviewers
Office machine operators
Receptionists
Secretaries, stenographers, typists
Telephone operators

05 Craftsmen
Apparel craftsmen and upholsterers
Bakers
Cabinetmakers
Construction craftsmen
Carpenters
Excavating, grading, and road machine operators
Electricians
Masons and tile setters
Painters, construction and maintenance, paperhangers
Plasterers and cement finishers
Plumbers and pipe fitters
Foremen
Linemen, servicemen (telephone, power)

05 (continued)
Locomotive engineers and firemen
Mechanics and repairmen
Metal craftsmen, except mechanics
Printing craftsmen
Stationary engineers, power station operators

06 Operatives (except transport)
Assemblers
Bottling and canning operatives
Checkers, examiners, inspectors (manufacturing)
Dressmakers, seamstresses
Garage workers and gas station attendants
Graders and sorters, manufacturing
Laundry and drycleaning operatives
Meat cutters and butchers
Mine operatives
Packers and wrappers, except produce
Painters, manufactured articles
Precision machine operatives
Sawyers
Sewers and stitchers
Stationary firemen
Textile operatives
Welders and flamecutters

07 Transport equipment operatives
Bus drivers
Taxicab drivers and chauffeurs
Truck drivers and deliverymen

08 Laborers (except farm)
Construction laborers
Freight, stock and material handlers

09 Farmers and farm managers

10 Farm laborers, foremen, unpaid family workers

11 Service workers (except private household)
Cleaning service workers
Food service workers
Health service workers (practical nurses, aides, orderlies, attendants)
Personal service workers
Protective service workers (firemen, policemen, watchmen)

12 Private household workers

13 Not in work force (unemployed are to be classified to their occupation)

APPENDIX G

MANUAL OF OPERATIONS

PULMONARY FUNCTION TESTING

I. DIFFUSING CAPACITY

A. Methods and Equipment

1. Single breath diffusing capacity ($D_L CO$) will be measured, but specific equipment is not specified. The carbon monoxide analyzer may be an infrared, fuel cell, or chromatograph device. The helium analyzer must be linear.
2. Test Gas: 0.3% CO, 10% He, 21% O_2 (or sea level equivalent for the same PiO_2, and the balance N_2). If a chromatograph is employed, neon may be used instead of helium for measurement of alveolar volume and 0.5% CO may be used for the test gas.
3. Special Considerations
   a. Leaks
      - The system must be checked daily. No change in volume of the pressurized system is required.
   b. Absorbers
      -Prior to every test, the CO_2 and H_2O absorbers must be checked and both changed if either more than ½ exhausted.
   c. CO Analyzers
      (1) Must be warmed up to maximum stability prior to use.
      (2) Calibration (±5%)
         (a) Linear Devices: Must be calibrated with test gases of at least two different known CO concentrations with fresh air as the zero. One of the calibrating gases should contain 0.3% CO and the other a lesser concentration. The system should be flushed completely and checked for zero after each test gas calibration.
         (b) Alinear Devices: A calibration curve must be constructed for the meter. This should be accomplished from known dilutions of the test gas. Chromatographs must also be calibrated by dilution techniques. Each sample is delivered through the reservoir bag. The actual CO concentration at each dilution is calculated and plotted against the meter reading (usually as % full scale). For all testing, the CO meter gain should be adjusted so the reference gas gives the same value as on the initial calibration. The analyzer should be completely recalibrated monthly. Calibration curves should be dated and retained at each center.
   d. Helium Analyzer
      (1) The device should be left on continously if used frequently
      (2) Calibration
         - Should be calibrated in conjunction with the CO analyzer. (linearity for chromatographs should also be documented for neon using dilution method).

Linearity should be tested using 100% and known dilutions of 10% helium in the CO mixture used for CO analyzer calibration. Complete calibration should be done monthly. Before each study, the meter should be checked against the reference gas.

e. Washout Volume
- The volume exhaled before collecting the alveolar sample should be as close to 750 ml as possible. (Centers using the PK Morgan Automated System will set the washout volume at 700 ml). If the patient's vital capacity is less than 1.2 liters, then 600 ml is used.

f. Alveolar Sample
- The standard goal will be 650 ml (600 ml for PK Morgan Automated Systems). If the vital capacity is low, the volume collected may be reduced to 400 ml. For Centers using the Collins Modular Lung Analyzer System with Gaensler-Smith 5-way Automated Valve P-1219, the electronic time delay for collection of the alveolar sample should be set at 3 seconds. If the vital capacity is too low to achieve 400 ml, the test will not be done with the notation "patient too ill".

g. Breathholding Time
- For Centers measuring D_LCO with manual bag in box or Collins Modular systems, the duration of breathhold is from the onset of inhalation to start of alveolar sample collection. (Olgivie, et al; Journal of Clinical Investigation 36: 1-7, 1967.). At Centers using automated PK Morgan units, breathholding time begins after "wash in" of a volume equal to the washout volume and ends after collection of one-half of the alveolar sample. With either system breathholding time should approximate 10 seconds. The expiration command should usually be given about 9 seconds from onset of inspiration. During breathholding the patient should breathhold, not rest against the shutter.

h. Reproducibility
- One of the major variables in D_LCO is the lung volume at which diffusion occurs. Consequently, attention must be directed at reaching TLC. Routinely, the Data Center will calculate D_LCO as the average of three maneuvers. The inspiratory vital capacity (STPD) for each diffusing capacity test will be reported. D_LCO values will be used only from tests in which the patient achieves at least 90% of the slow vital capacity (corrected to STPD) measured on spirometry. If none of three procedures achieve the required volume, the result is the one from the biggest vital capacity. The test is never repeated more than twice.

B. Procedures

1. Exact details vary with manufacturer of equipment. General principles may be reviewed in Clinical Pulmonary Function Testing published by the Intermountain Thoracic Society, 1975. Investigators at Centers with the Collins system and Gaensler-Smith automated valve should review the report of Gaensler and Smith. (Chest 63: 136, 1973.).
2. General Guidelines
   a. With nose clipped, have the subject breathe normally through the mouthpiece until relaxed. A rubber mouthpiece with phlanges should be used.
   b. Instruct the patient to exhale slowly to residual volume, then the patient is switched into the test gas circuit. Inhalation then proceeds rapidly to TLC.
   c. After 9 seconds of breathholding, instruct the patient to exhale rapidly to residual volume.
   d. After 750 ml (700 ml for the PK Morgan System) are exhaled, the next 650 ml (600 ml for the PK Morgan System) is collected for gas analysis (the Alveolar Sample).
   e. The subject is detached from the apparatus.
   f. The test is repeated twice, waiting 5 minutes between each procedure.

C. Measurements

1. Barometric pressure (Pb) and spirometer or room temperature in °C.
2. From the spirogram -
   a. Vital capacity (VC) corrected to STPD
   b. Breathholding time (t in sec)
3. From the 0.3% CO calibration curve
   - Expired CO (CO_E) as concentration in percent.
   Inspired CO (CO_I) should be 0.3%
4. From the He meter readings
   a. Inspired concentration of helium in per cent (He_I).
   b. Expired concentration of helium in per cent (He_E).

D. Calculations

VC_____mls STPD

t_____secs

CO_I .03 %

CO_I_____%

He_I_____%

He_E_____%

Pb_____mmHg

PiO_2_____mmHg

$$VAml = VC \cdot \frac{He_I}{He_E}$$

$$CO_{Ao} = CO_I \times \frac{He_E}{He_I}$$

$$D_LCO = \frac{VA\,ml \times 60\ sec/min}{t\ sec\ \ (Pb - 47mmHg)} \times LN \cdot \frac{CO_{Ao}}{CO_E}$$

$$D_LCO = \text{\_\_\_\_\_} \ ml/min/mmHg$$

Where: PiO_2 = partial pressure inspired O_2 (should approximate 150 mmHg)

CO_{Ao} = initial alveolar CO concentration

VA = alveolar volume (TLC at STPD)

II. SINGLE BREATH NITROGEN WASHOUT

A. Methods and Equipment

1. Two options

a. A bag in box system as drawn in the enclosed schematic from the July, 1973 National Heart and Lung Institute pamphlet: Suggested Standardized Procedures for Closing Volume Determinations (Nitrogen Method) may be used. An x-y recorder may be used instead of an x-y-y recorder if flow is displayed to the patient on another recorder either via galvanometer or strip chart. Since flow volume curves and lung volumes are not measured, valve #5 is optional. The alinear resistance is optional but expiratory flow must be below 0.5L/sec. (Figure 1)

b. A waterless electric spirometer capable of differentiating volume signals to flow may be filled with 100% oxygen. Oxygen is delivered to the patient from the spirometer and oxygen tank equipped with a Robertshaw demand valve or equivalent apparatus. Inspired and expired volume are measured by the spirometer. Flow must be displayed to the patient and kept below 0.5 L/sec on expiration.

2. The nitrogen meter must be rapid responding and linear. If used, the x-y or x-y-y plotter must be rapid responding. Expired volume, flow, and nitrogen concentration may be recorded on a four channel strip chart recorder rather than an x-y device since closing volume is not to be determined. A two channel recorder may be used if flow is displayed elsewhere as by galvanometer.

3. A low resistance 3 or 4 way valve (#3 in the schematic) is required in both systems.

B. Procedure

1. Preparation

a. Nitrogen meter calibration
-Calibrated with dry gas samples of known concentration (may be tonometered or calibrated commercial tanks).
(1) Daily: Two points of known dry gas concentration (0 and 80% N_2).
(2) Monthly: Against dry N_2 gas concentration of 0,5,10,50, and 80%.

b. If the spirometer is used for the supply of oxygen, it should be filled with oxygen and emptied through the

inspiratory lines and valves three times to flush out all air from tubing and valve dead space. The spirometer should then be filled with 5 to 7 liters of 100% oxygen in preparation for the test. If the balloon in box system is used, the balloon should be filled and all tubing and inspiratory valves filled with 100% oxygen.

c. Explain the procedure and adjust the mouthpiece for the seated patient. Place the nose clips.

2. The Nitrogen Washout Procedure
- The following are performed twice at least 5 minutes apart.

Step 1: The subject should take a deep breath, then, be instructed to exhale to residual volume. The patient hand signals when empty.

Step 2: Encourage the subject to inhale maximally from the 100% oxygen source. The rate of flow need not be controlled.

Step 3: Without breathholding, the subject exhales from TLC at $\leq$ 0.5L/sec to residual volume.

C. Measurements

1. Expired nitrogen concentration and expired volume must be recorded. If plotted on an x-y recorder, N_2 is on the ordinate and volume on the abscissa. The slope of Phase III is determined by calculating the change in per cent N_2 concentration between 750-1250 ml expired volume.
2. The test is repeated once. Exhaled N_2 must be within 2% of baseline before starting the second measurement.
3. The average of the two determinations is the reported result for Slope of Phase III.

III. PLETHYSMOGRAPHY

A. Methods and Equipment:

1. The technique of Dubois, et al using shallow rapid breathing will be employed. (J. Clin. Invest. 35:322, 1956 and ibid 35:327, 1956). The principles of plethysmography for standardization of technique outlined by David Leith and Jere Mead in National Heart and Lung Institute, Division of Lung Diseases Pamphlet: Principles of Body Plethysmography, November, 1974, are basically those for this study. In edited form, this report is outlined here.

a. Absolute Thoracic Gas Volume
- The airway is obstructed by means of a solenoid-operated valve in a mouthpiece assembly while the subject attempts to breathe alternately expanding and compressing the gas within the respiratory system. With the glottis open, mouth pressure equals alveolar pressure since no gas flow occurs. The pressure difference across the closed mouthpiece shutter is displayed on the ordinate of an oscilliscope and the associated change in body volume (due to compression and decompression in the lungs) as reflected by pressure changes in the plethysmograph on the abscissa. The slope of the mouth pressure - plethysmograph pressure (box) is the volume of gas undergoing compression. Thus, the total volume of gas subjected to compression is then calculated by multiplying the slope of the resulting line of mouth pressure versus

plethysmograph pressure (i.e., volume change) by the barometric pressure minus water vapor pressure at body temperature. (Assumes that alveolar gas is always saturated with water vapor at body temperature).

b. Airway Resistance
-The relationship between airflow and the associated pressure drop along the airways is the desired measurement. The subject pants through a pneumotach at a lung volume to be measured as above. Any thoracic volume changes not due to gas flow at the mouth must be due to compression or expansion of gas in the lung. Since the subject breathes to and from the box, the plethysmograph measures only the latter volume changes. (Other pressure changes such as warming and cooling of respired gas are minimized by the panting maneuver). Since the thoracic gas volume at which panting occurs is also measured, these volume changes may be used as a measure of alveolar pressure changes so that the pressure drop along the airways for the measured flow (by pneumotach) can be determined. Plethysmograph pressure is plotted on the abscissa versus flow on the ordinate of the oscilloscope.

2. The following equipment is required:
   a. Constant volume variable pressure plethysmograph with pressure transducer capable of measuring pressure changes calibrated to volume changes of ± 100 ml at 2 cps. The box pressure transducer should be calibrated prior to each test, using a pump which generates a known gas volume. A "flow-box"-transmural-breathing pressure/volume plethysmograph may be used.
   b. Mouthpiece assembly with solenoid controlled shutter and pneumotach inside the plethysmograph. The pneumotachs used in this study in plethysmography and lung mechanics must be calibrated daily. Pneumotachs will be calibrated by flow meters linear ± 1% full scale. A 0-3L/sec meter will be used for low flow pneumotachs.
   c. Differential pressure transducer for mouth pressure sensitive to ± 20 cm H_2O.
   d. Electronics and split function oscilloscope for display of two x-y plots (mouth pressure vs. box pressure and flow vs. box pressure).
   e. Oscilloscope gradicule to read slope or tangent of the described angle of the x-y displays.
   f. For "flow-boxes", the mouth pressure transducer, the mouth flow meter and the box flow meter should be calibrated prior to each test in conjunction with phase compensation of the box. The accuracy of volume measurements should be tested using isothermal bottles at least daily.

B. Procedure
1. The subject is seated in the plethysmograph and familiarized with the test. The patient should be seated comfortably with feet on the floor. The mouthpiece is adjusted so that the patient's chin will be slightly extended.
2. Weight Correction
-If the electronics are so equipped, correction for patient's size may be accomplished by dialing in the patient's weight. Alternatively, allowance for the subjects body volume can be done with the subject seated in the plethysmograph. While the subject breathholds, a known volume of air is pumped into the

3. Each of the following maneuvers will be repeated at least 3 times and the results averaged.
   Step 1: The patient sighs and breathes quietly. At the end of a normal expiration, the mouth shutter closes and the subject pants at about once per second (2 cps) over and over so that the slope of the line can be accurately estimated. FRC can then be calculated.
   Step 2: Next the patient pants at about 1 liter/sec (2 cps) through the unobstructed mouthpiece assembly and the slope (or angle tangent) of the line, flow vs. box pressure is estimated. In severely obstructed patients, the described line (or loop) may develop great box pressure changes in relation to flow changes. In such cases, the slope should be read between flows of 0.5 liters/sec. The slope should be read as the line of best fit through the average of the loop.
   Step 3: At the end of an expiration on the above panting, the shutter closes and the subject again pants over and over at about once per second for the calculation of Vtg. Airway resistance is calculated from the data generated in Steps 2 and 3.

C. Measurements:
1. Barometric pressure (Pb)
2. From the average of at least 3 maneuvers for each variable -
   a. Slope (or angle tangent) of mouth pressure vs. box pressure (λ 1) after end of normal expiration (for FRC).
   b. Slope (or angle tangent) of flow on rapid panting vs. box pressure (λ 2) (for airway resistance).
   c. Slope (or angle tangent) of mouth pressure vs. box pressure (λ 3) when shutter closed on point of zero flow on above panting maneuver (for Vtg).

D. Calculations:

$$FRC = \frac{(Pb\ mmHg - 47) \times 1.36 \times \text{box calibration factor (ml/cm)}}{\lambda\ 1 \times \text{mouth pressure calibration } (cmH_2O/cm)}$$

$$Raw = \frac{\lambda\ 3 \times \text{mouth pressure calibration } (cmH_2O/cm)}{\lambda\ 2 \times \text{flow calibration}}$$

$$Vtg = \frac{(Pb\ mmHg - 47) \times 1.36 \times \text{box calibration factor (ml/cm)}}{\lambda\ 3 \times \text{mouth pressure calibration } (cmH_2O/cm)}$$

IV. SPIROMETRY

A. Methods and Equipment
- A volume displacement spirometer is required. A hard copy of the volume-time trace is essential. The spirometer must be capable of accumulating volume over the entire forced expiration.

B. Procedures
- Nose clips are recommended.
1. Slow Vital Capacity (VC)
   - Performed with subject seated
   a. After several breaths to establish FRC, the subject inspires maximally to TLC then exhales maximally to RV. Repeat once. Inspiratory capacity (IC) and slow vital capacity are calculated

b. After FRC is established, the subject inspires maximally to TLC. Repeat once. The slow vital capacity is calculated.

2. Forced Vital Capacity (FVC)
- The forced vital capacity will be performed at least three times but not more than six (6) times. Acceptable curves will be those with smooth continuous exhalation with apparent maximal effort and without the following discredits defined by the American Thoracic Society - Snowbird Workshop on the Standardization of Spirometry held January 18, 1977 at Snowbird, Utah.
   a. Coughing
   b. Valsalva
   c. Early termination of expiration. Forced expiration must continue for at least 6 seconds.
   d. A leak
   e. Obstructed mouthpiece. (including dentures and subject's tongue)
   f. Unsatisfactory start. Back extrapolation to time 0 on the volume time tracing must be less than 10% of the FVC.
   g. Excessive variability between the three acceptable curves. The two best FVC's on the three acceptable curves must not vary more than ± 10% or 200 ml, which ever is greater.
3. The spirometer should be flushed with fresh air between each maneuver.

C. Measurements
- Recorded in BTPS
1. Slow Vital Capacity
   a. VC is the largest of the four valves.
   b. IC is the larger of the two valves.
2. Forced Vital Capacity
   - FVC, FEV_1, $FEF_{25-75\%}$ will be determined. The single "best curve" is defined as the curve with the largest algebraic sum of FVC and FEV_1. The FVC and FEV_1 from each of three acceptable curves (as defined above) will all be sent to the DATA Center. These measurements may be determined by computer or by hand calculations. The $FEF_{25-75\%}$ will be determined from the best curve.
3. Spirometry is repeated after bronchodilator challenge.

D. Calibration
1. Volume is calibrated by giant syringes. Must be independent of flow rate. Accuracy must be within ± 50 ml.
2. Time(strip chart recorder) is checked by 60 cycle electrical ocillations. For kymographs, time calibration is performed by running the drum on rapid setting for a minimum of 10 seconds checked by stop watch. For x-y recorders, time is also checked by stop watch for 10 seconds.

E. Helium - Oxygen Spirometry ($He-O_2$)
- Optional. Results not reported to DATA Center. Guidelines are suggestions except that no more than three forced vital capacities should be performed to avoid patient fatigue. If $He-O_2$ spirometry is performed, air spirometry should also be recorded on an x-y or x-y-y recorder as flow volume curves.

1. Methods: Data should be recorded on a rapid responding x-y or x-y-y recorder as flow versus volume curves. Data may be stored on a computer for subsequent playback. The gas mixture should contain 80% helium and 20% oxygen.
2. Procedure: With subject seated and nose clipped, a three minute breathing period on the He-O_2 should precede standing forced expiratory maneuvers. Expired gas during washout should be measured for N_2 and the three minute period extended if exhaled N_2 concentration excedes 5%. The patient is turned back to He-O_2 breathing until three FVC maneuvers are accomplished.
3. Measurements: The FVC must agree within 200 cc with air spirometry.
   a. FEF 75%, 50%, 25%
   b. Viso $\dot{v}$ (volume of iso flow). The best air and best He-O_2 curve should be used and superimposed at TLC.
   c. The testing should be repeated after bronchodilator challenge.

V. LUNG MECHANICS

A. Methods: The technique outlined by Peter Macklem in the National Heart and Lung Institute, Division of Lung Diseases Pamphlet: Procedures for Standardized Measurements of Lung Mechanics will be followed. Pertinent, modified sections are reproduced below. Lung volumes may be measured by spirometer at the mouth or by volume displacement plethysmograph.

B. Procedures:

1. Measurements of Esophageal Pressure

   a. Esophageal Balloon

   Hyatt type balloons, 10 cm long and #200 polythylene tubing 100 cm long with multiple holes in the distal 9 cm covering the balloon will be employed.

   b. Positioning of Balloon

   The empty balloon, passed through the nasopharynx, is swallowed into the stomach. Topical anesthesia to the nasal mucosa and pharynx is optional, but usually unnecessary.

   Introduce about 0.5 cc of air into the balloon and connect it to the pressure transducer.

   If the balloon is in the stomach, the pressure will become more positive during inspiration. If the pressure moves in a more negative direction, the balloon is in the esophagus. What is important is the direction of the pressure swings, not the absolute pressures. This should be tested by having the subject sniff repeatedly. Pull back the balloon cm by cm until the pressure swings in the negative direction. The upper part of the balloon is now in the esophagus.

   Pull the balloon back 10 cm more. The whole balloon is now in the esophagus and close to its final position; i.e., where the tip of the balloon should be 10-15 cm from the stomach.

The final position is determined by adjusting the balloon to the point where the end-expiratory pressure is most negative and the cardiac artefact is least. (A marker in the polyethylene tubing 45-50 cm from the tip of the balloon is of great help in locating the balloon tip). In general, the balloon tip should be between 35-45 cm (usually 38-42 cm) from the nares.

Always record the balloon position. Always remove the catheter with the balloon empty.

Once the balloon is in position, check for the tracheal artefact as follows:

Display to the subject an aneroid or water manometer connected to the mouthpiece.

With the mouthpiece occluded, have the subject generate pressures of ± 10 cm H_2O as recorded by the anaeroid manometer at a frequency of about 0.5 cps.

Transpulmonary pressure (i.e., esophageal minus mouth pressure) should remain constant. If it does not, the balloon is in the region of the tracheal artefact and should be advanced until the artefact disappears.

c. Calibration
- Transducer for esophageal balloon should be calibrated prior to each test. The mouth pressure transducer should be calibrated at least daily.

d. Adjusting Air Volume
- Ideally a double ground 10 cc glass syringe should be used, but any airtight syringe in which the plunger slides freely in the barrel can be used. Connect the syringe to the balloon via a 3-way stopcock at the transducer. Stopcocks are potential sources of leak and should be checked beforehand.

Have the subject perform a series of forceful coughs or, if he is trained, Valsalva's manuever. This will empty the balloon.

Hold the plunger of the syringe so that the balloon does not refill. Turn the stopcock so that the balloon is closed. Fill the syringes with 8 cc of air.

Inject 8 cc of air into the balloon and withdraw 7.5 cc. Turn the stopcock so that the balloon is connected to the transducer.

e. Trouble Shooting
- Zero pressure must be checked frequently. Balloon volume must be retested at the end of the procedure. If a leak has occurred, measurements must be repeated. Changes in the zero baseline are due to instabilities of the

electronic recording equipment, improper balancing of the pressure transducer, or movement of the transducer.

External leaks will cause increasing balloon volume because the pressure in the balloon catheter system is subatmospheric.

If the balloon loses volume, this almost always means a hole in the balloon. Leaking balloons can usually be avoided by distending the balloon under water prior to insertion.

If an external leak is present, connect the syringe directly to the balloon and, by pulling on the plunger, determine if the leak is within the catheter itself. If not, work backward step-by-step, adding connectors and stopcocks and testing for leaks as each component is added, until the source of the leak is found.

Be careful not to exert a large negative pressure if the pressure is applied to the transducer.

A frequent source of leaks is the junction of the catheter with its metal adaptor, where the tubing can kink and may crack.

If the balloon volume is small, the volume displacement characteristics of the balloon catheter system may be such that the balloon empties itself during forced expirations and no longer accurately transmits pressure. When this occurs, the pressure tracing becomes flat. The solution is to put more air in the balloon. However, this only becomes a problem if one is interested in measuring esophageal pressure during cough or forced expiration; i.e., when pressures are positive.

To obviate artefactual change in balloon volume during respiratory efforts, the balloon catheter should be attached directly to the pressure transducer not connected by long external tubing.

If esophageal pressures look fine during spontaneous breathing, but "funny" (generally too positive) during static P-V curve measurements, the mouth pressure port of the transducer may be open to the atmosphere.

If esophageal pressures are becoming more positive, check for (1) leaks into the balloon and (2) balloon position.

If pressures look damped, first check to see that the preamplifier is not on "average". If this is not the trouble source, the catheter may be kinked, which can be checked by seeing if air moves freely in and out of the catheter.

If the recording pen seems always to move in the same direction regardless of whether the pressure is going positive or negative, the switch on the preamplifier may be set to "cal" rather than "use".

2. Measurement of Lung Mechanics
-Static Pressure-Volume Curves

FRC must be determined if volume changes are measured at the mouth in a constant volume variable pressure plethysmograph as described in III, Plethysmography.

Mouth pressure relative to esophageal pressure is used as an index of transpulmonary pressure. Volume is measured with a spirometer or by whole body plethysmography.

In order to control volume history, the volume changes should be displayed to the subject on an oscilliscope or by some mechanical means. During quiet breathing, mark FRC on the display and, on full inspiration, mark TLC. Attention must be directed at establishing and recording a stable FRC. The subject inspires to TLC, expires to FRC, reinspires slowly to TLC. This volume history maneuver is repeated once, then the subject reinspires slowly to TLC and expires slowly to RV. On the latter maneuver, the mouthpiece is repeatedly occluded for 1-2 seconds so that the expiration proceeds in a stepwise fashion.

Expiratory static pressure-volume curves are obtained by plotting lung volume against the simultaneously recorded plateau of transpulmonary pressure during periods of zero airflow.

At least three repeatable curves should be obtained.

C. Measurements
- From three maneuvers, pressure-volume curves will be constructed by line of best fit. Lung recoil will be determined at TLC, 90%, 80%, and 70% TLC and at FRC in cm H_2O.

D. Outline of Testing and Special Considerations
1. Balloon inserted. Position recorded. For subsequent testing balloon position should be identical.
2. Subject placed in plethymograph. After several sighs FRC measured as described in Section III.
   a. If variable volume plethysmograph used for determination of lung volume, measurements will be made in the box but procedure is otherwise as described below.
   b. If a spirometer is used for measurement of changes in lung volume, the subject is moved to a nearby spirometer immediately after determination of FRC. The spirometer tubing must be equipped with a mouth shutter and pressure transducer. Simultaneous permanent calibrated recording of volume-time and transpulmonary pressure-time tracings is required.
3. Balloon volume adjusted to 0.5 ml of air. Balloon volume must be rechecked at the end of testing. If a leak has occurred measurements must be repeated.

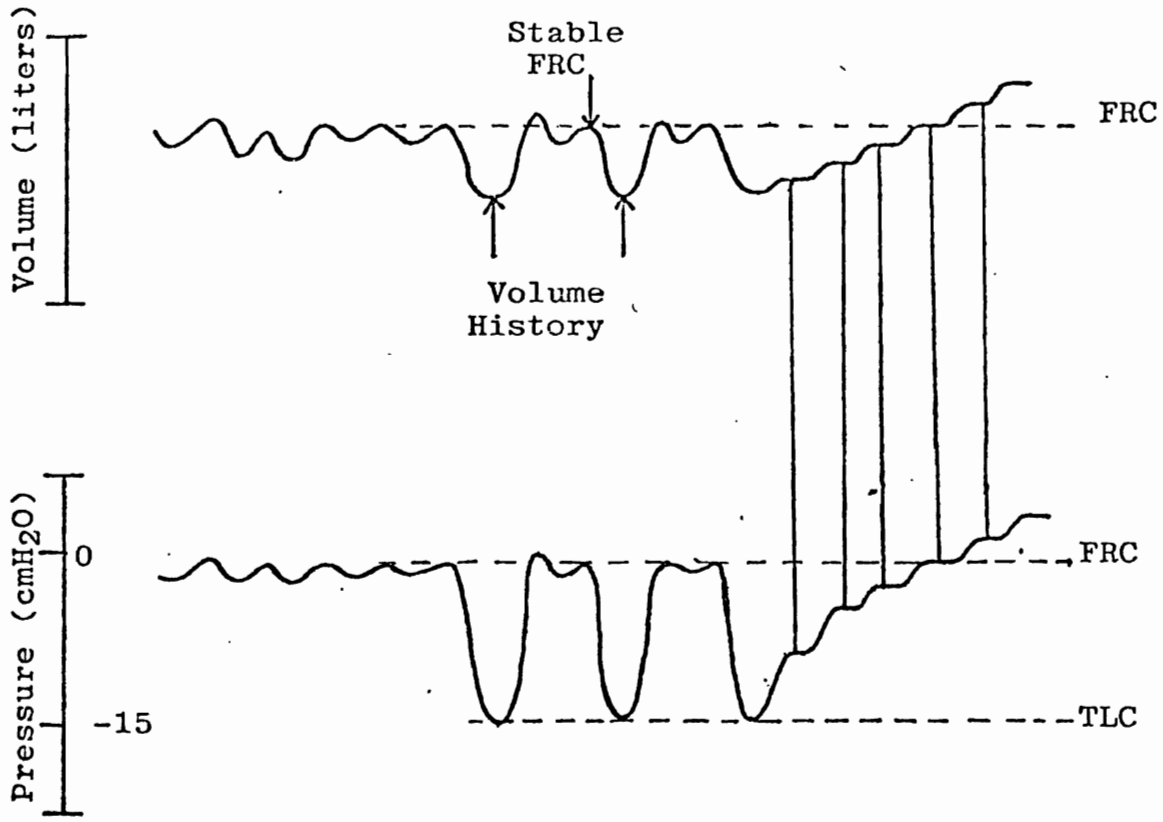
4. Volume history insured prior to each determination by two inhalations to TLC.
5. Stable FRC established as in plethysmograph. Volume and transpulmonary pressure must be recorded during volume history and FRC breathing.
6. Subject inhales from FRC to TLC. On slow exhalation to RV the mouthpiece shutter is closed periodically for 1-2 secs.
7. Expiratory pressure-volume data are plotted from three acceptible curves.

E. Construction of Pressure Volume Curves
- Professional review of raw data is required to insure that reported data are valid.

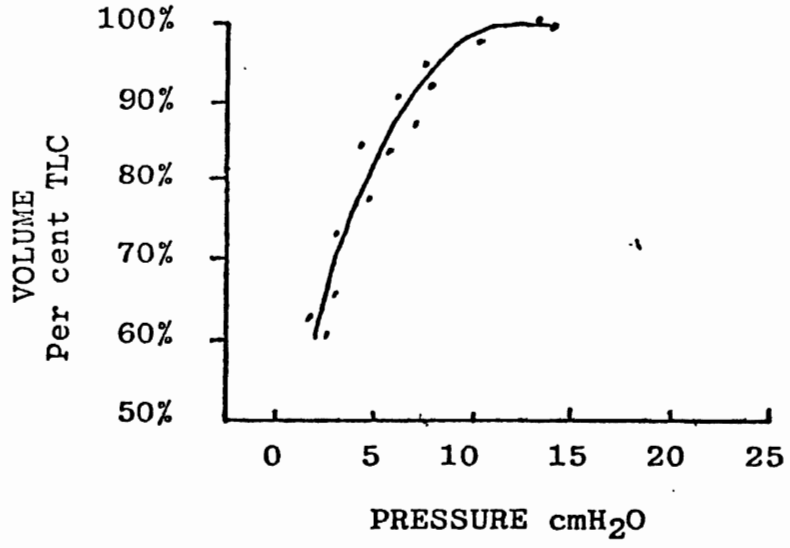
1. Checks for reliable curves.
   a. Pressure at TLC during volume history maneuvers should closely approximate the value at TLC on the static deflation maneuver.
   b. The inspiratory capacity from stable FRC should agree (±200 ml) with the IC obtained from spirometry (Section IV).
2. Plotting Pressure-Volume Curves.
   a. Transpulmonary pressure on the abscissa is plotted versus lung volume as per cent TLC on the ordinate. FRC will be used as the reference volume. All valid data points from the three reporducible curves are plotted.
   b. The Expiratory Pressure-Volume curve is drawn as the line, by eye, of best fit.
   c. Lung recoil, determined from the curve, is recorded at TLC, 90%, 80%, and 70% TLC and at FRC. Measurements below FRC are suspect and need not be recorded.

F. Examples:

1. Tracings



2. Pressure-Volume Curve



VI. EXERCISE TESTING PROTOCOL

A. Methods and Procedures

1. Pretest Conditions
   -Subjects must be fully recovered from any other testing including prolonged psychometric studies as well as physically tiring tests. No meal should be taken within the preceding two hours of exercise.
2. Cycle Ergometer
   a. Any cycle ergometer may be used.
   b. Calibration
      -For electromechanical cycle ergometers, a cycle calibrator is essential. All cycles should be calibrated metabolically every month using one normal person. The same individual should be used for serial testing. Metabolic calibration is done by measuring oxygen consumption (VO_2) and heart rate for the last 15 seconds of 3 minute exercise at 200, 400, 600 KPM from which a calibration curve is constructed. Results should be ± 10%. Calibration curves should be saved at each center.
3. A physician must be present during all exercise testing.
4. Phase I - One Minute Increment Test
   a. Sequence
      (1) After electrocardiograph (EKG) electrodes are applied, the subject sits on a calibrated electromechanical cycle ergometer. The saddle is adjusted so that the knee is near full extension at the bottom of the pedal stroke. The EKG must be monitored continuously during exercise and until recovery. Expired gas is collected at rest and during exercise.
      (2) After accommodation to the cycle, pedalling begins at 100 kpm. Each minute, exercise demand is increased by 100 kpm. Time is controlled by stop watch.
   b. Exercise End Points
      (1) Symptoms
         -Intolerable dyspnea or fatigue, chest pain, severe dizziness, confusion.
      (2) EKG changes
         (a) HR>180/min
         (b) Ventricular arrhythmias, paroxysmal atrial tachycardia, development of atrial fibrillation, second or third degree heart block or evidence of myocardial ischemia.
5. Phase II-Steady State Exercise and Gas Exchange
   a. Sequence
      (1) Subjects rest until completely recovered from Phase I defined as return to basal HR (within 5 beats/min) and pre-exercise symptoms. An arterial cannula placed into a radial or brachial artery is optional. The EKG leads are reapplied. The subject then relaxes on the cycle, and the saddle is readjusted.
      (2) At rest, sitting on the cycle, an arterial blood sample is obtained <u>after</u> resting HR is recorded for one minute. Respiratory rate (f) is counted before

blood drawing.

(3) Exercise

(a) Subjects pedal at 60 ± 20 rpm for 5 minutes at the work load equivalent to a VO_2 of 800 ml/min. Time is controlled by stop watch. The EKG is continuously monitored. Expired gas is collected for the last minute of exercise. Arterial blood gases are drawn approximately 30 seconds after gas collection begins.

(b) Subjects unable to achieve 400 kpm workload in Phase I will perform steady state exercise free wheeling.

(c) Expired gas will also be collected from 3-4 minutes of exercise but analyzed and reported only for those patients unable to complete 5 minutes of steady state exercise.

B. Measurements

-Phase I

1. Heart rate (HR)
   -Heart rate (beats/min) is calculated from continous monitor at rest and at the end of each exercise level.
2. Ventilation
   -Minute ventilation (liters/min, BTPS) is determined from the expired gas collection at rest and for the last 20 seconds of each exercise work load. Respiratory rate (breaths/min) is measured at the end of each exercise level.
3. Maximum level of exercise
   -Maximum power output achieved for an entire minute where each 100 kpm increment is termed a level so that level 1 = 100 kpm, level 2 = 200 kpm, etc. Subjects unable to pedal a full minute will be recorded as achieving level 0. Resting measurements listed below should be made prior to Phase I.

-Phase II

a. Heart rate (HR) at rest and exercise. The latter is recorded as the average EKG rate at the beginning and end of the last minute of cycle pedalling.
b. Respiratory rate (f) at rest and exercise. For exercise, f should be determined from a strip chart recording of end tidal CO_2 or pneumotach signal, or from a Tissot spirometer. Reported f is the average rate at the beginning and end of the last minute of exercise.
c. Expired gas may be collected in either a Tissot spirometer or Douglas Bags (hung vertically). Oxygen and CO_2 concentration in the expirate will be measured.
d. The arterial blood samples drawn at rest and 4½ minutes of exercise will be analyzed for paO_2, and pH.
e. From these measurements expired minute ventilation (BTPS), oxygen consumption (STPD), carbon dioxide production (STPD), dead space to tidal volume ratio, and alveolar-arterial oxygen gradient (mmHg) will be calculated at rest and for the last minute of exercise.

C. Protocol for Patients on Supplemental Oxygen

-When patients are deemed candidates for continuous oxygen supplementation, they return for complete evaluation. Part of this evaluation includes exercise testing. This initial re-evaluati will include exercise testing breathing room air and supplemental oxygen.

1. Subjects able to exercise without O_2
   a. Perform Phase I and II on room air
   b. Repeat Phase I breathing nasal O_2 at 2 L/min.
2. Subjects unable to exercise without O_2
   - Initial assessment for continous oxygen
     Phase I - breathing air.
     Phase I - breathing nasal O2 at 2 L/min.
3. Serial Studies
   - Those subjects able to perform Phase I exercise (i.e., complete at least Level 1, 100 kpm) breathing air although on home oxygen will be serially tested breathing air and oxygen. Those subjects unable to exercise without O_2 will be serially tested only breathing O_2.

VII. ARTERIAL BLOOD GASES

A. Methods and Equipment

1. Either brachial or radial artery puncture will be used. Local anesthesia is optional but the patient must have rested quietly for at least 5 minutes.

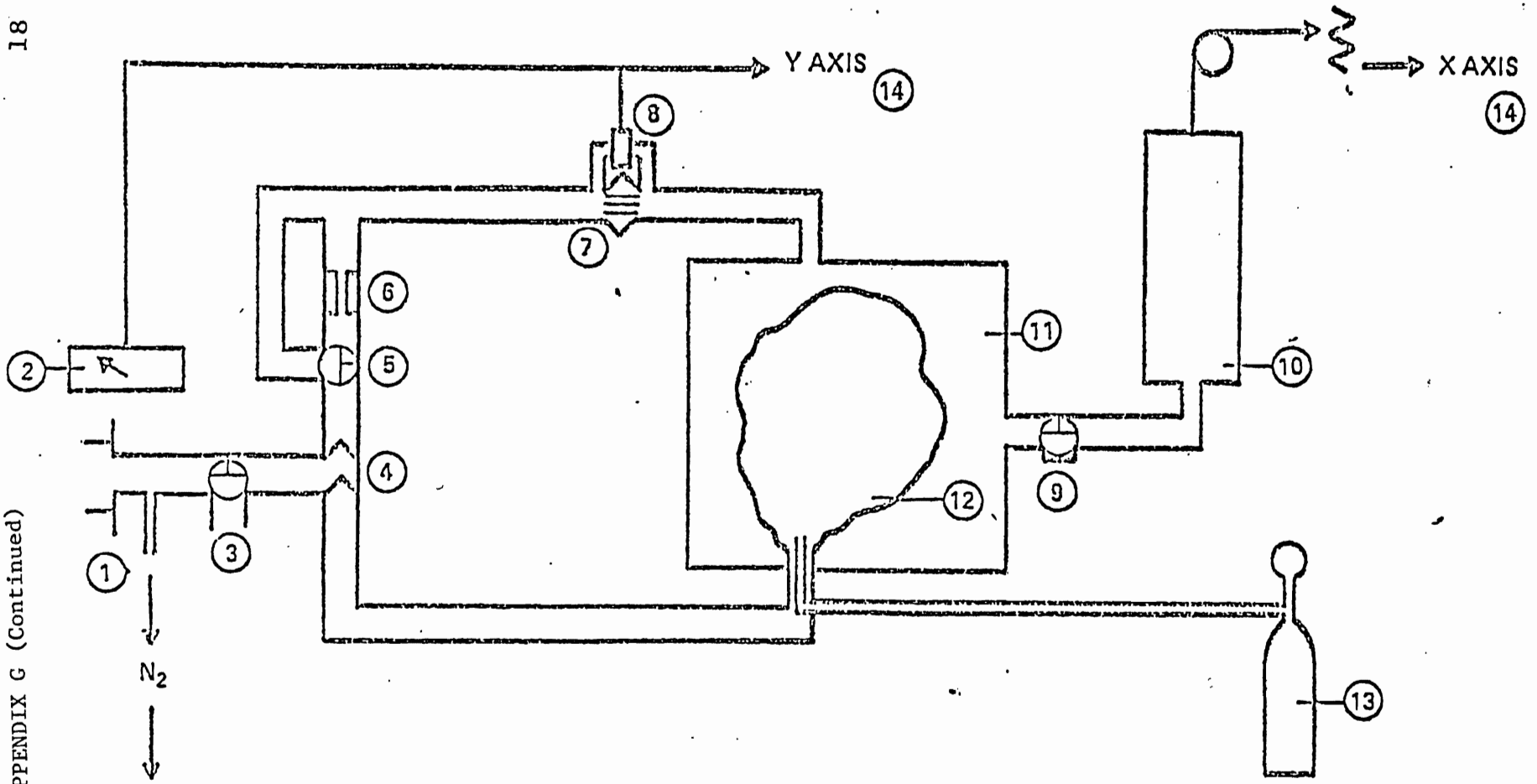
2. The type of blood gas analyzer is not specified but it must be accurately calibrated. Calibration will be done periodically throughout each day with commercial precalibrated gas mixtures

   The device must also be calibrated at least weekly with tonometered blood.

B. Measurements

- paO_2, $paCO_2$, pH will be measured immediately or if refrigerated within 30 minutes of collection.

Figure 1. ,EQUIPMENT SCHEMATIC



LEGEND

(See text for complete description)

1. MOUTHPIECE WITH NITROGEN METER SIDE PORT
2. GALVANOMETER FOR FLOW DISPLAY
3. 3-WAY VALVE
4. BREATHING VALVE-ONE WAY
5. 3-WAY VALVE
6. ALINEAR RESISTANCE
8. DIFFERENTIAL TRANSDUCER
9. 3-WAY VALVE
10. 9 L. SPIROMETER
11. 35 L. BOX
12. 30 L. RUBBER BAG
13. OXYGEN SUPPLY
14. XYY RECORDER

APPENDIX H

NORMAL FLORA

1. Alpha hemolytic streptococcus
2. Nonhemolytic streptococcus
3. Neisseria species (excluding gonorrhoeae and meningococcus)
4. Corynebacterium species (excluding C. diphteriae)
5. Lactobacillus species
6. Micrococcus species
7. Staphylococcus epidermidis
8. Haemophilus species (excluding influenzae)

APPENDIX H (Continued)

NATIONAL NOSOCOMIAL INFECTIONS STUDY

REVISED PATHOGEN LIST AND CODE

I. BACTERIA

CODE FIELDS 1-2-3	GENUS	SPECIES	COMMENTS
- - -	No culture obtained, culture lost		
0 1 0	Culture obtained, no pathogen isolated		
0 1 1	Culture obtained, results pending		
0 1 2	Culture obtained, organism not identified		
3 2 0	Acinetobacter	sp.	
3 2 1		calcoaceticus, var. lwoffi	Mima polymorpha
3 2 5		calcoaceticus, var. anitratus	Herrellea, B. anitratum
3 4 0	Achromobacter	sp.	
3 4 1		xylosoxidans	
5 1 0	Actinobacillus	sp.	
4 0 0	Actinomyces	sp.	
4 0 1		bovis	
4 0 2		israelii	
4 0 3		naeslundii	
4 0 4		odontolyticus	
4 0 5		viscosus	
1 0 6	Aerococcus	sp.	
3 5 5	Aeromonas	sp.	
3 7 0	Alcaligenes	sp.	
3 7 1		denitrificans	
3 7 2		fecalis	
4 0 9	Arachnia	propionica	
2 1 7	Arizona	sp.	
1 4 0	Bacillus	sp.	
1 4 1		anthracis	
1 4 2		subtilis	
1 4 3		cereus	

CODE FIELDS 1-2-3	GENUS	SPECIES	COMMENTS
4 1 0	Bacteroides	sp.	
4 1 1		corrodens	prefer Eikenella corrodens, 380.
4 1 2		fragilis	
4 1 3		melaninogenicus	
4 1 4		oralis	
4 1 5		pneumosintes	
4 1 6		putredinis	
5 2 7	Bartonella	sp.	
5 2 8		bacilliformis	bartonellosis
4 3 0	Bifidobacterium	sp.	
5 3 0	Bordetella	sp.	
5 3 1		bronchisepticum	
5 3 2		parapertussis	
5 3 3		pertussis	whooping cough
5 5 0	Borrelia	sp.	relapsing fever
5 2 0	Brucella	sp. (incl. suis)	brucellosis
5 2 1		abortus	"
5 2 2		canis	"
5 2 3		melctensis	"
3 6 5	Cardiobacterium	hominis	
3 5 0	Chromobacter	sp.	
2 2 6	Citrobacter	sp.	
2 2 7		diversus	
2 2 8		freundii	
4 2 0	Clostridia	sp.	
4 2 1		botulinum	botulism (toxin)
4 2 2		tetani	tetanus
4 2 3		difficile	
4 2 4		histolyticum	
4 2 5		limosum	
4 2 6		novyi	
4 2 7		perfringens	
4 2 8		septicum	
3 8 5	Colymnatobacterium	granulomatis	granuloma inguinale

CODE FIELDS 1-2-3	GENUS	SPECIES	COMMENTS
5 0 0	Corynebacterium	sp.	"diphtheroids"
5 0 1		bovis	
5 0 2		diphtheria	diphtheria
5 0 3		mitis	
5 0 4		pyogenes	
5 0 5		ulcerans	
5 0 6		xerosis	
2 0 5	Edwardsiella	sp.	
2 0 6		tarda	
3 8 0	Eikenella	sp.	
3 8 1		corrodens	cf. Bacteroides corrodens, 411
2 4 0	Enterobacter	sp.	
2 4 1		aerogenes	
2 4 2		agglomerans	
2 4 3		cloacae	
2 4 4		hafniae	prev. Hafnia
1 9 0	Erwinia	sp.	
5 1 4	Erysipilothrix	sp.	
2 0 0	Escherichia	coli	
2 0 1		coli, enterotoxin producing	
4 3 4	Eubacterium	sp.	
4 3 5		lentum	
4 3 6		limosum	
3 6 0	Flavobacterium	sp.	
3 6 1		meningosepticum	
3 6 2		II-B	
6 0 3	Francisella	sp.	
6 0 4		tularensis	tularemia
4 4 0	Fusobacterium	sp.	
4 4 1		fusiforme	
4 4 2		mortiferum	
4 4 3		necrophorum	
4 4 4		nucleatum	
4 4 5		varium	

CODE FIELDS 1-2-3	GENUS	SPECIES	COMMENTS
1 0 7	Gaffkya	sp.	
1 6 0	Gemella	haemolysans	
5 9 0	Hemophilus	sp.	
5 9 1		ducreye	
5 9 2		influenzae	
5 9 3		parainfluenzae	
2 3 0	Klebsiella	sp.	
2 3 1		ozaenae	
2 3 2		pneumoniae	
2 3 3		rhinoscleromatis	
1 4 7	Lactobacillus	sp.	
5 4 0	Leptospira	sp.	
5 4 1		autumnalis	
5 4 2		ballum	
5 4 3		canicola	
5 4 4		georgia	
5 4 5		pomona	
5 4 6		pyogenes	
5 4 8		icterohemorrhagiae	
1 5 0	Listeria	sp.	
1 5 1		denitrificans	
1 5 2		grayii	
1 5 3		ivanovs	
1 5 4		monocytogenes	listeriosis
1 5 5		murrayi	
1 0 5	Micrococcus	sp.	
3 3 0	Moraxella	sp.	
3 3 1		bovis	
3 3 2		kingii	
3 3 3		lacunata (liquefaciens)	
3 3 4		nonliquefaciens	
3 3 5		osloensis	
3 3 6		phenylpyruvica	

CODE FIELDS 1-2-3	GENUS	SPECIES	COMMENTS
6 1 0	Mycobacterium	sp.	
6 1 1		tuberculosis	tuberculosis
6 1 2		bovis	
6 1 3		Group I	atypical mycobacteria
6 1 4		Group II	" "
6 1 5		Group III	" "
6 1 6		Group IV	" "
6 1 7		leprae	leprosy
5 7 0	Neisseria	sp.	
5 7 1		catarrhalis	
5 7 2		flava	
5 7 3		gonorrhoeae	gonorrhea
5 7 4		lactamicus	
5 7 5		meningitidis	meningococcal disease
4 9 5	Nocardia	sp.	
6 0 0	Pasturella	sp.	
6 0 1		multocida	
1 9 5	Pectobacterium	sp.	
4 5 0	Peptococcus	sp.	
4 5 1		asaccarolyticus	
4 5 2		prevotti	
4 6 0	Peptostreptococcus	sp.	
4 6 1		anaerobius	
4 6 2		facultative	
4 6 3		intermedius	
4 6 4		magnus	
3 5 8	Plesiomonas	shigelloides	
4 7 0	Propionibacterium	sp.	
4 7 1		acnes	
4 7 2		granulosum	
2 6 0	Proteus	sp.	
2 6 1		mirabilis	
2 6 2		morgagni	
2 6 3		rettgeri	
2 6 4		vulgaris	

CODE FIELDS 1-2-3	GENUS	SPECIES	COMMENTS
2 7 0	Providencia	sp.	
2 7 1		alcalifaciens	
2 7 2		stuartii	
3 0 0	Pseudomonas	sp.	
3 0 1		aeruginosa	
3 0 2		acidovorans	
3 0 3		cepacia	
3 0 4		fluorescens	
3 0 5		maltophilia	
3 0 6		pseudomallei	
3 0 7		putida	
3 0 8		stutzeri	
2 1 0	Salmonella	sp.	
2 1 1		typhi	typhoid fever
2 1 2		cholerae-suis	
2 1 3		enteritidis	all other serotypes; >1000 recognized
1 0 4	Sarcina	sp.	
5 5 5	Selenomonas	sp.	
2 5 0	Serratia	sp.	
2 5 1		liquefaciens	
2 5 2		marcescens	
2 5 3		rebideae	
2 2 0	Shigella	sp.	
2 2 1		boydii	
2 2 2		dysenteriae	
2 2 3		flexneri	
2 2 4		sonnei	
5 1 9	Spirillum	sp.	
1 0 0	Staphylococcus	sp.	
1 0 1		aureus	coagulase +
1 0 2		epidermidis	coagulase -
1 0 3		salivarius	
5 1 7	Streptobacillus	sp.	

CODE FIELDS 1-2-3	GENUS	SPECIES	COMMENT
1 1 0	Streptococcus	sp.	
1 1 1		viridans	
1 1 2		Group A	
1 1 3		Group B	
1 1 4		Group C	
1 1 5		Group E	
1 1 6		Group F	
1 1 7		Group G	
1 1 8		Group H	
1 1 9		Group K	
1 2 0		Group L	
1 2 1		Group M	
1 2 2		Group N	
1 2 3		Group O	
1 2 4		Group P	
1 2 5		Group Q	
1 2 6		Group R	
1 2 7		Group S	
1 2 8		Group T	
1 2 9		Group U	
1 3 3	Streptococcus	pneumoniae	Pneumococcus Diplococcus pneumoniae
1 3 4	Streptococcus, Group D	unspecified	
1 3 5		bovis	
1 3 6		equinus	
1 3 7		faecum	
1 3 8		durans	
1 3 9		faecalis	enterococcus
5 6 0	Treponema	sp.	
5 6 1		pallidum	syphilis
5 6 2		pertenue	yaws
4 5 5	Veillonella	sp.	
4 5 6		alkanescens	
4 5 7		parvula	
5 8 0	Vibrio	sp.	
5 8 1		alcaligenes	
5 8 2		cholerae	cholera
5 8 3		fetus	
5 8 4		parahemolyticus	
5 8 5		sputorum	

CODE FIELDS 1-2-3	GENUS	SPECIES	COMMENTS
3 4 5	Xanthomonas	sp.	
6 0 6	Yersinia	sp.	
6 0 7		pestis	plague
6 0 8		enterocolitica	
6 0 9		pseudotuberculosis	

V. FUNGI

CODE FIELD 1-2-3	GENUS	SPECIES	COMMENTS
	More Common and Major Pathogenic Fungi		
8 0 0	Aspergillus	bispora	
8 0 1		flavus	
8 0 2		fumigatus	
8 0 3		oryzae	
8 0 4		niger	
8 0 7	Blastomyces	dermatitidis	
8 1 0	Candida	sp.	
8 1 1		albicans	
8 1 2		guillermondi	
8 1 3		drusei	
8 1 4		pseudotropicalis	
8 1 5		rugosa	
8 1 7	Coccidioides	sp. (imitis)	
8 1 8	Cryptococcus	sp.	
8 1 9		neoformans	
8 2 0	Histoplasma	sp. (capsulatum)	
8 2 1	Mucor	sp.	mucormycosis; opportunistic
8 2 2	Sporothrix (Sporotrichum)	sp. (schenckii)	sporotrichosis
8 2 3	Torulopsis	sp.	granulomas in anima
	Less Common Pathogenic Fungi		
8 3 0	Actinomadura	sp.	
8 3 1	Agromyces	"	
8 3 2	Allescheria (Monosporium)	"	mycetoma
8 3 3	Alternaria	"	
8 3 4	Aureobasidium	"	
8 3 5	Bacterionema	"	

CODE FIELD 1-2-3	GENUS	SPECIES	COMMENTS
8 3 6	Basidiobolus	sp.	entomophthoromycosis
8 3 7	Beauvaria	"	
8 3 8	Cephalosporium (Acremonium)	"	
8 3 9	Chrysoporium	"	
8 4 0	Cladosporium	"	chromoblastomycosis; brain abscess
8 4 1	Curvalaria	"	
8 4 2	Dactylaria	"	
8 4 3	Dermatophilus	"	
8 4 4	Drechsleria	"	
8 4 5	Entomophthora	"	entomophthoromycosis
8 4 6	Epidermophyton	"	
8 4 7	Fonseca	"	chromoblastomycosis
8 4 8	Fusarium	"	keratomycosis
8 8 1	Geotrichum	"	
8 4 9	Helminthosporium	"	
8 5 0	Hyphomyces	"	
8 5 1	Leptotrichia	"	
8 5 2	Loboa	"	
8 8 0	Madurella	"	mycetoma
8 5 3	Microbispora	"	
8 5 4	Micromonospora	"	
8 5 5	Micropolyspora	"	
8 5 6	Microsporum	"	tinea capitis

CODE FIELD 1-2-3	GENUS	SPECIES	COMMENTS
8 5 7	Mortierella	sp.	
8 5 8	Neurospora	"	
8 5 9	Nigrospora	"	
8 6 0	Paracoccidioides	"	
8 6 1	Penicillium	"	
8 6 2	Phialophora	"	chromoblastomycosis, mycetoma
8 6 3	Phoma	"	
8 6 4	Piedraia	"	
8 6 5	Pityrosporum	"	tinea versicolor, blepharitis, etc.
8 6 6	Prototheca	"	
8 6 7	Pyrenochaeta	"	one agent in maduromycosis
8 6 8	Rhinosporidium	"	
8 6 9	Rhizopur	"	mucormycosis; opportunistic
8 7 0	Rhodotorula	"	transient fungemia 2° IV's; low pathogenicity
8 7 1	Rothia	"	
8 7 2	Saccharomyces	"	
8 7 3	Sepedonium	"	
8 7 4	Streptomyces	"	
8 7 5	Syncephalastrum	"	
8 7 6	Thermoactinomyces	"	
8 7 7	Thermopolyspora	"	
8 7 8	Trichophyton	"	tinea cruris, pedis, & capitis; ringwo

CODE FIELDS 1-2-3	GENUS	SPECIES	COMMENTS
8 8 2	Trichosporon	sp.	highly pathogenic in experimental animal
8 7 9	Ustilago	"	
8 9 9	Other or Unidentified sp.		

APPENDIX I

Guide to reading Chest Radiographs for I.P.P.B. Study

Form 714.0

C. Lung Volumes

1. Lung Height - Record the length of a vertical line from the posterior (or highest) inferior margin of the first rib to a horizontal line passing through the dome of the diaphragm.

2. Lung Height - Record the rib whose anterior end is at or just above the level of the right hemidiaphragm.

3. Diaphragm is - at or below the rib.
This is an attempt to further refine this visual impression (#2)

4. Lung width: Record the length of a horizontal line at the level of the right dome of the diaphragm from the interior margin of the ribs of the right to the interior margin of the ribs of the left hemithorax.

5. Retrosternal air space -
Measuring along the sternum locate a point 3 cm. down from the manubrial-sternal joint. Record the distance from this point along a horizontal line to the anterior portion of the ascending aorta.

6. Sternal Diaphragmatic angle -
On the lateral chest film measure the angle of the intersection of the sternum and the diaphragm. Choose an appropriate length of sternum and diaphragm to give a representative angle.
(see illustration)

D. Bullae: -

Bullae are defined as partial or completely outlined thin walled air containing cavities.

E. Pulmonary Vessels -

1. Right descending: Record the diameter of the right descending artery in its most proximal non-curved portion (see illustration).

2. Left Descending - On the lateral radiograph locate the left main stem bronchus (point A) and the posterior wall of the left descending artery as it turns around the left main bronchus. Record the smallest distance from the inner wall of the bronchus to the outer (or posterior) wall of the artery (see illustration)

This artery may not be visible on every patient. Please record 99 for missing value.

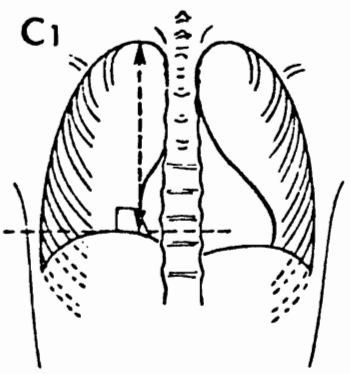
3. Peripheral vascular pattern -
The reader is to estimate whether or not the vascular pattern is normal, or abnormal based on his own impression of normality.

Factors to be considered are the number, attenuation and distortion of vessels in a region that would represent vessel loss compatible with emphysema. Other vascular abnormalities Ex. A.V. malformation should be recorded under "G" other significant findings.

F. Heart Size -

1. Transverse diameter of heart. Record the largest horizontal diameter of the heart on the P.A. chest film.

2. Widest intrathoracic diameter. Record the largest diameter on the P.A. chest film measuring from the interior edge of the ribs on the right to the interior edge of the ribs on the right hemithorax.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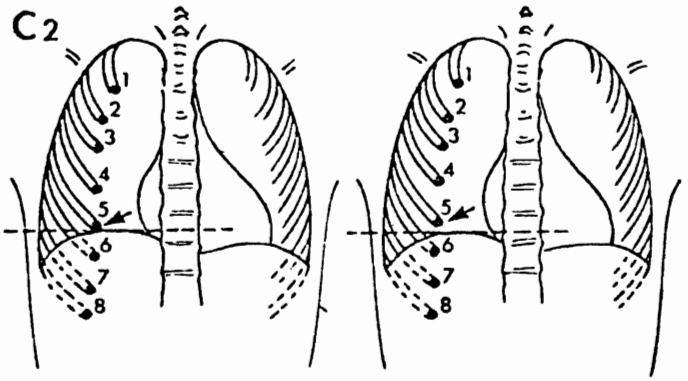
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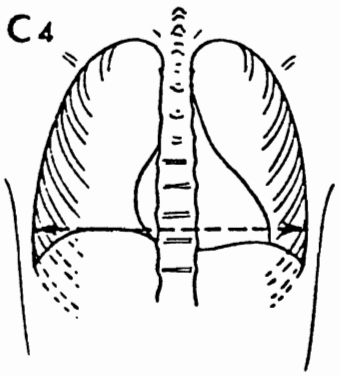
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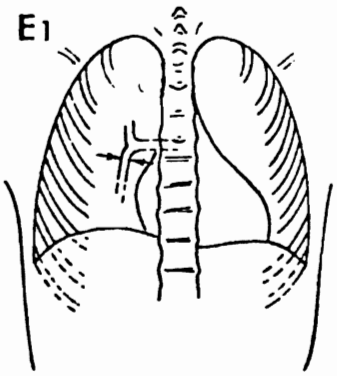
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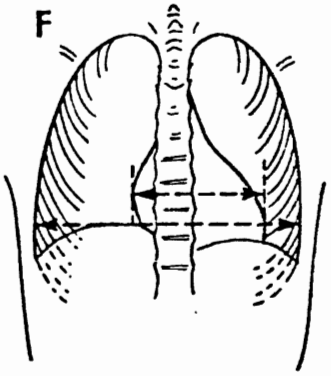
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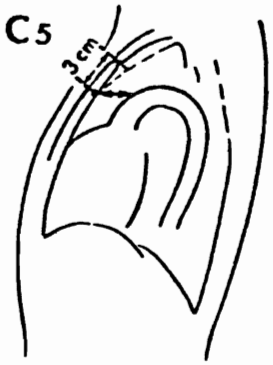
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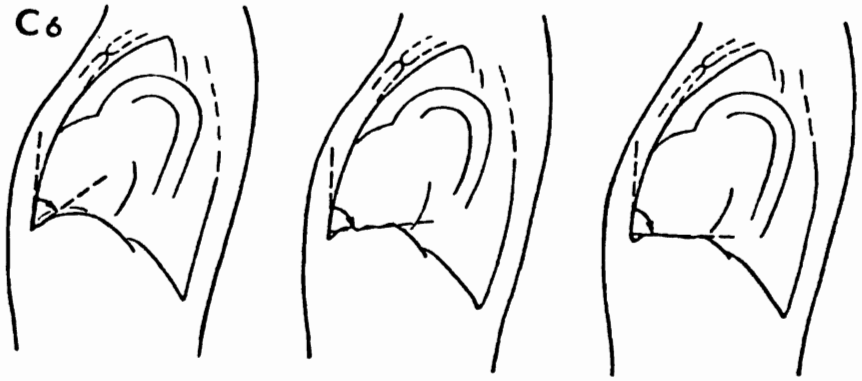
C6

APPENDIX J

Sickness Impact Profile

Clinical Study of IPPB

INSTRUCTIONS TO THE RESPONDENT

Before beginning the questionnaire, I am going to read you the instructions.

You have certain activities that you do in carrying on your life. Sometimes you do all of these activities. Other times, because of your state of health, you don't do these activities in the usual way: you may cut some out; you may do some for shorter lengths of time; you may do some in different ways. These changes in your activities might be recent or longstanding. We are interested in learning about any changes that describe you today and are related to your state of health.

I will be reading statements that people have told us describe them when they are not completely well. Whether or not you consider yourself sick, there may be some statements that will stand out because they describe you today and are related to your state of health. As I read the questionnaire, think of yourself today. I will pause briefly after each statement. When you hear one that does describe you and is related to your health please tell me and I will check it.

Let me give you an example. I might read the statement, "I am not driving my car." If this statement is related to your health and describes you today, you should tell me. Also, if you have not been driving for some time because of your health, and are still not driving today, you should respond to this statement.

If you are in the hospital today, you are here because of your state of health, and you are not doing a number of the things you usually do. For instance, if driving is usual for you, then you are not driving today because you are in the hospital, and you should respond to this statement.

On the other hand, if you never drive or are not driving today because your car is being repaired, the statement, "I am not driving my car" is not related to your health and you should not respond to it. If you simply are driving less, or are driving shorter distances, and feel that the statement only partially describes you, please do not respond to it.

I am now going to begin the questionnaire. Please tell me if you want me to slow down, repeat a statement, or stop so that you can think about one. Also let me know any time you would like to review the instructions. Remember we are interested in the recent or longstanding changes in your activities that are related to your health.

APPENDIX K

SICKNESS IMPACT PROFILE

INTERVIEWER TRAINING MANUAL

DECEMBER, 1977

Introduction to Standardized and Structured Interviewing

The Sickness Impact Profile questionnaire is designed to be administered in a standardized and structured interview format. In the administration of a standardized and structured questionnaire, the questions themselves, the way in which they are asked, and their order are predetermined. The reason for standardization is to insure that all respondents are describing themselves according to their understanding of the same statement. Supplementary questions are not asked. No extraneous comments concerning the questionnaire items are given by the interviewer, nor are subjects allowed to modify the wording of items. The purpose behind this format is simple and straightforward: to eliminate as completely as possible any biasing effect an individual interviewer might have on a subject's responses. In other words, the goal of the standardized interview in general and the goal of this training in particular is that different interviewers could interview the same subject and provide the same picture of his behavior within the limits only of subject variability from one time to another.

Obviously, no two interviewers are alike. People coming into this job will differ in age, sex, education, background, skill, appearance, personality, life-style, etc. The focus of acquiring skill and training as an interviewer is to neutralize these differences as much as possible in terms of their affect on subjects. Becoming an interviewer means taking on a professional role and this by definition may necessitate making changes in one's appearance, manner, etc., while occupying this role. For example, an interviewer's dress should be neutral. Avoid wearing costumes which loudly proclaim a certain socio-economic status, political or curtural bias, etc. Don't overdress for encounters in which a person with a lower socio-economic status might be "turned off."

An interviewer's manner should be warm but distant. It is extremely important to establish rapport with a subject in order to motivate him to

participate. At the same time you job is to record information. You should give the subject the impression that you are interested in him but are not personally interested in his responses to the questionnaire. This warm-but-distant role is not one that most of us use regularly. Therefore, you may find that it takes some effort and concentration before it will feel comfortable and appear natural.

Consider for the moment that "warm" and "distant" are end-points on a single continuum. It appears from considerable observation of interviewers that a tendency to behave in a manner characteristic of either extreme is counterproductive. The overly warm, solicitous interviewer may inadvertently encourage the subject to respond to items in a effort to please. This could easily result in an inflated score. On the other hand, the excessively distant or withdrawn interviewer may discourage responses as the subject's motivation may wane if he feels the interviewer has no interest in him. Observation of other interviewers as well as feedback from observation of your own practice interviews should enable you to develop an appropriate and comfortable interviewing style.

The following is a list compiled by L.E. Borg ( ) of the qualities most essential in interviewers. It seems a fitting conclusion to the preceding discussion.

Qualities Required for Interviewing

1. A genuine love for people regardless of the respondent's economic status in life.
2. A thoroughly honest approach in handling every assignment.
3. An above average intelligence, sprinkled with a conscientious attitude.
4. A 100 percent neutral attitude on any subject matter when interviewing.
5. The ability to be adaptable under any circumstances among any group of people.
6. A mastery of readable longhand writing.

Qualities Required for Interviewing cont.

7. A friendly, unhurried attitude with respondents, yet the ability to conduct the interview in a businesslike manner.
8. The ability to follow instructions to the letter.
9. The capability of reading all questions exactly as worded.
10. A strict adherence to avoiding, as much as possible, any personal judgment as to what the person is trying to say.

Borg reference:

Borg, L.E., Interviewing School. International Journal of Opinion and Attitude Research 2(3):393-400, Fall 1948.

Introduction to the Sickness Impact Profile

The Sickness Impact Profile (SIP) is a behaviorally-based measure of health status which may be used for:

1. Assessment of the health of populations
2. Evaluation of medical care programs
3. Evaluation of treatment programs
4. Planning and program development
5. Individual patient assessment

Impacts of sickness are often expressed in the way people behave, or the way they carry out their daily activities. For example, they may cut out some activities; they may do some for shorter lengths of time; they may do some in different ways. The SIP is an instrument designed to measure these sickness-related changes in behavior, or "dysfunctions," as perceived and reported by the consumer of health services.

The SIP does not presume to measure capacity, i.e., whether or not a person in <u>able</u> to do something. Rather it is focused on behavior and is solely concerned with whether or not the person perceives himself as actually <u>performing</u> an activity.

Background of the SIP

The Sickness Impact Profile questionnaire you will be using is the result of five years of development and testing. Investigators started with 1200 descriptions of dysfunction reported by individuals who were sick and added to these behaviorial statements from existing function-assessment measures. Standard grouping and sorting techniques yielded 312 unique items or statements describing sickness-related behavioral changes. Each statement describes a behavior and specifies a dysfunction. The SIP has been tested in three field trials and revised subsequent to each trial. The final form contains 136 items grouped into 12 categories. Each category appears to describe either an area of living or a type of activity in which sickness-related dysfunctional behavior takes place. These areas of living include such things as social interaction, emotional behavior, ambulation, eating, etc.

The 136 items have been weighted or scaled as to the severity of the dysfunction each one describes. This task was performed by both health care professionals and consumers. The items were placed in relation to one another on a 15-point scale ranging from minimally dysfunctional to severely dysfunctional. As a result each item now has a corresponding weight or scale value and subject can be assigned dysfunction scores on the entire questionnaire or on individual categories or groups of categories.

As you will learn from studying the questionnaire, a subject is instructed to respond to any statements which he is sure describe him today and are related to his state of health. The subject responds to the questionnaire using himself as his own baseline. He is instructed to not respond to items describing activities which simply to not apply to him. He is further instructed to respond to a statement which describes a health-related change in his behavior even if the change has persisted over a period of time. In other words, a subject with a chronic condition would compare his present

Background cont.

behavior to what is would be (perhaps used to be) if his state of health were not a controlling factor.

Description of the Sickness Impact Profile Questionnaire

The following is a brief description of the SIP questionnaire.

1. Preceding the actual SIP items is a introduction which explains to the subject how he is to respond to the questionnaire.
2. The SIP items are grouped in twelve categories, each of which is related to an area of living or type of activity.* the items within each category are listed in a random order. Each group or category of items begins with a introductory statement.
3. Because of the randomization of items, each item in the questionnaire has two numbers. First, to the left of each item is a number which designates its position in the category. These start with number 1 at the beginning of each category. Second, to the right of the response line for each item is the SIP item number. For instance, the item "I stay alone much of the time" is always numbered 23 regardless of its position in the questionnaire. These SIP item numbers will be used for coding and scoring.
4. At the bottom of each page of the questionnaire is a line or box which must be checked to show that the items on that page have been read.

insert at * The categories are arranged within the SIP in a random order. In addition,

Suggested Responses to Questions Subjects May Ask

During your initial contact with a subject whether it a preliminary phone call or just prior to the interview, there are standard questions which may be raised. Here are the answers to some of them. You may find additional help in the Guidelines section at the end of your manual.

--If the subject asks about confidentiality, assure him that all information will remain strictly confidential, and that no record will be kept that identifies subjects by name. You may also tell him that none of the information he gives will go to his physician or his medical record.

--If the subject asks about the nature of the interview, explain that it is a simple checklist, involving no long or written answers, and that the questions require no specific knowledge, but are simply about his own activities.

--If the subject says he is too sick to be interviewed, you can suggest that the interview can be done with several breaks, so he won't get too tired. Assure him of how important his participation is to your study.

Preliminary to Interview

Do your interviews in a private, quiet place.

--Ask the subject if there is a quiet place where the two of you could go, since you will reading aloud and it is difficult to concentrate if others are present, explaining that you are required to interview subjects alone.

--Suggest that the subject turn off TV, radio, etc.

If you are offered a cup of coffee, etc., accept it (even if you don't drink it). This usually does a great deal to establish rapport.

ADMINISTERING THE SIP

Reading the Introduction

After obtaining a signed Consent Form, begin the interview by reading the introduction printed at the beginning of the questionnaire. If asked, you may give the subject a copy of the introduction to follow along. Please read the entire introduction exactly as it is written. Read it clearly and slowly to make sure the subject understands. Answer any questions the subject may have when you are finished by repeating appropriate phrases from the introduction. Maintain frequent eye contact with the subject while you are reading the introduction. This will help establish rapport and will also enable you to determine if you are being understood. (If at any time during the interview the subject asks a question you think is answered in the introduction, feel free to go back and reread the appropriate section to him.)

You will note that the instructions do not provide the subject with a specific response to use, e.g. yes, true, etc. This decision was made for two reasons. First, although "yes" and "true" are the responses most commonly selected by subjects, neither is a completely appropriate response to the SIP items, and it was impossible to discover a more appropriate alternative. Second, if it were recommended that subjects use "yes" to respond to items that describe them, this might imply a "no" response to inapplicable items, and might ultimately cause a verbal deliberation on each item. Since the goal was to elicit a response from a subject only to items that he was sure described him, it seemed most efficacious to emphasize this in the instructions and allow the subject to select the most appropriate or comfortable response.

Reading the Category Introductions

It is important that you always read the introductory statement at the top of each page before beginning the category or group of items. While some of these statements will provide additional information about the items to follow, their primary function is to reemphasize for the subject the three important criteria for response he must remember while considering each of the items. In other words these statements remind him that he should respond to an item if:

he is sure it describes him (1) today (2) and is related to his state of health. (3)

You may find that reading these introductory statements becomes repetitive. Therefore, it is particularly important that you remember to read each one slowly and with the proper emphases. This is a good opportunity to have eye contact with the subject and an excellent opportunity to SMILE.

Reading the Items

1. Read every item to the subject exactly as written.
2. Read the items clearly and slowly.
3. Pause briefly between the items so that the subject has enough time to respond.
4. Concentrate on the items as you read them, that is, think about what each one is saying.
5. Emphasize the key words in an item, i.e., the words that may distinguish it from other items, for example,

   I walk more slowly

   I walk only with help from someone

6. Remember that each subject is hearing the questionnaire either for the

first time, or after a significant length of time from his last interview.

7. Be careful not to speed up your pace, or to develop a monotone toward the end of the interview.
8. Do not look up while reading the items unless the subject asks a question, or until a category is completed. At the same time, be aware of the subject at all times, and look up if you feel he may be inattentive, puzzled, etc.
9. Show interest in the subject, but do not give the impression that you approve or disapprove of any answer the subject gives, that you are surprised or shocked at any answer he gives, or that you have a special interest in hearing his answer to any specific question.

Remember that your relationship with the subject should be relaxed and non-threatening, that you should appear interested in him, but impersonal and somewhat distant, so that he will not feel any embarrassment in telling you how he is behaving. Keep in mind that you will be asking some sensitive and personal questions. Practice on friends and relatives to be sure that you expression and tone of voice will not make the subject uncomfortable. Avoid making the subject feel that he should respond to any items except those that he is sure really describe him. It is also important not to give the impression that there are certain items that he shouldn't respond to.

An interviewer's neutrality should go beyond maintaining a neutral facade. Avoid making assumptions about a subject's behavior or developing expectations about specific responses. This is important for three reasons:

1. If you do make assumptions or have expectations this information can be very easily communicated to the subject;
2. If the subject does not respond according to your expectations, you are likely to become frustrated and assume that the interview is invalid;

3. Any assumptions you make (in spite of how obvious they seem to you) could easily be incorrect.

Since it may be difficult for you to accept this third point, here are a couple of examples:

--A subject who is bedridden with an acute illness who does not respond to "I am going out for entertainment less often" may never go out for entertainment even when perfectly healthy.

--An amputee who does not respond as you would expect to "I do not walk at all" may, in fact, do so with the help of prosthetic devices.

and the list goes on.

Remember your functions as an interviewer are to: (1) motivate the subject to participate; (2) ensure that the subject understands the instructions and remains aware of them throughout the interview; (3) allow the subject an opportunity to respond to each item; and (4) record the subject's responses completely and accurately. Beyond reviewing instructions when appropriate (specific situations are outlined in the Guidelines section at the end of your manual) you should not influence a subject's responses in any way.

Conducting an Interview with Breaks

Occasionally during an interview you may have a subject who becomes tired or is not paying attention, so that continuing with the interview is difficult or unwise. You should suggest a break of about 10 minutes before continuing. If the break is suggested because you believe the subject is tiring, it can be suggested in this manner: "I think my voice needs a rest. Would you mind a few minutes' break?" Or: "I'd like to stop for a few minutes for a drink of water (rest). Is that all right with you?" If the subject is unwilling to accept a break that is that short, offer to complete the interview later that day after he has had time to rest.

Once an interview is started, it must be completed within 24 hours. Remind the subject of how important his participation is to the success of your project.

Recording ~~Item-Data~~ Subjects' Responses

1. As you read each item to a subject, make a mark by the code number next to the response line. In this way, you are sure you have read all of the the items and if you are interrupted, you will know where to begin again.
2. Place a "1" on the response line when a subject indicates that an item does describe him. We will be giving you methods for dealing with questions and subjects' uncertainties about responding to items. The important thing to remember here is that you should only record a "1" for an item that a subject is sure describes him.
3. Leave the response line blank whenever a subject does not respond to an item.
4. If the subject cannot understand an item or refuses to consider it for any reason, record a "9" (no information) on the response line.
5. After you have read all of the items on the page, put a check in the box in the lower-right hand corner. This provides you with a quick check at the end of the interview that no page has been skipped and all the items have been read.

Recording Comments, Questions, and Problems

As you read the questionnaire, you may also be asked to record any comments made by the subject about the items. Questions, criticisms, and other specific comments about the items should be written in the spaces between the items.

If you think a subject's response to an item is highly unlikely, inconsistent with other responses, unrelated to health, etc., record the response as given. Then, put an asterisk next to the item so that you can note your comment at a later time.

After you leave the subject, record your comments about asterisked items. You may also with to fill out an Interviewer Comment Sheet. The Interviewer Comment Sheet should be used to record problems you may have had in arranging or conducting the interview, comments about the subject's behavior that might affect the interpretation of the responses, comments about the interview or items in general that might help someone to understand this interview or to revise the SIP questionnaire. You might also record any positive or negative comments the subject may make about the interview or the study in general.

You may also wish to keep a section in your notebook to record any general comments about items or problems with interviews that you would like to have discussed at field meetings.

Guidelines for Dealing with the Unexpected

In past field trials with the SIP information has been gathered from interviewers about events that have occurred during interviews that have been a problem for them. Ways of handling these situations have been developed and are described below. As other situations arise for you, it may be necessary to make some additions to the quidelines.

First, four basic things to keep in mind in any interview:

A. Remember that the subject is a very important person, and you must deal with everything that concerns him during the interview.

B. When the subject expresses a concern, accept his concern and restate it to show that you do understand the problem.

C. Help the subject to understand that you cannot change the interview or the wording of the statements and assure him that his comments and questions are important and will be considered in improving the questionnaire. Remember to record these comments.

D. Express appreciation to the subject for his cooperation.

Here are some guidelines for specific situations:

1. Subject answers or interrupts before you finish reading the statement. If he responds positively, repeat and complete the statement, although you may omit the examples. If the subject answers negatively or asks a question, repeat the entire statement.

2. Subject gives a response that you do not believe is related to his health. If the subject seems sure of his response and raises no question about it, you should record a "1". Do not ask if it is related to his health. You may put an asterisk next to the statement to remind you to note on your comment sheet that you believe that he may have answered incorrectly.

If the subject has a question about how to respond to a statement, says that is describes him sometimes, that he has always done that, etc., then you should repeat the introductory statement for that category and then reread the statement. Do not ask directly if it is related to his health.

3. Subject changes his response.

   You may make a correction anytime the subject requests it. (Cross off checks as opposed to erasing them.)

4. Subject refuses to answer a statement.

   Code a "9" (no information). Do not try to convince the subject to consider the statement.

5. Subject responds "yes" or "no" to all statements.

   Repeat to him that he need respond only to those statements that he is sure describe him. If he continues to respond to all statements, let him do so.

6. Subject objects to continuing the interview because he says it doesn't apply to him.

   Say: "We've interviewed many people who aren't sick, and you'd be surprised how many find statements that apply to them." Also, "People often find it interesting to hear the kinds of statements people do say describe them and are related to their state of health."

7. Subject objects to a particular group of statements because he thinks they won't apply to him.

   Tell him that you have to read all of the statements to every subject. You may use the statement listed in #6.

8. Subject believes the statement was read before.

   This may occur when similar items are asked. Assure the subject that all the statements are different. You may show him a statement that you read

earlier which is similar.

9. Subject doesn't understand a statement.

Repeat it exactly, do not define or interpret statements. If the subject still doesn't understand, say "I am not able to explain the statement in any way since we must read exactly the same statements to everyone. If it isn't clear to you, it may not be clearly written. I will note your question and we will skip this statement and go on to the next one." Record a "9" for that statement.

10. Subject may ask to read the statements to himself.

Explain that you have been instructed to read them to every subject, in order to keep all the interviews the same, even though it takes more time. Add that the subject may read along with you if he wishes and move to his side so that he can read them with you or offer him a blank set of statements.

11. Subject asks what we are doing with the information.

Explain that his answers will be combined with those of other people to provide information about the appropriateness of the questionnaire statements and the usefulness of such descriptive information to people offering health care.

12. Subject isn't sure whether a behavior is related to his health.

Explain that this is his decision, but remind him that "we are interested in things that you are sure describe you and are related to your state of health today."

13. Subject says a statement describes what others say about him.

Explain that we are only interested in the way he sees his own behavior, not what he's heard other people say; if he is sure a statement describes him, he should respond to it.

14. Subject indicates that he thinks you know all about him or his condition.
Make it clear that you know nothing about him or his health, and ask that he respond to the statements with this in mind.

15. Subject, in a conversational comment, mentions to you changes in his activities that he did not respond to during the interview.
Do not change his interview answers, but note this on an Interviewer Comment Sheet.

16. Subject asks for your help in responding to a statement.
Explain that it is his decision and remind him that "we are interested in things that you are sure describe you and are related to your state of health today."

17. Subject complains that a statement or group of statements is too personal.
Explain that many people do describe themselves in these ways and suggest that often personal aspects of our lives are affected by our health. Remind the subject that you are just a recorder and that all information he gives is confidential.

18. Subject suggests that the wording of a statement be changed.
Tell him that you will note his suggestion but right now he may only consider the statement as you have read it.

19. Subject discusses his illness, symptoms, or medical care.
Do not encourage a conversation about the subject's health, for example, just answer with a nod or smile or "um hum". If the subject continues, tell him that you are not a medical person and would not know what to do about his problem. Be sure that you do not offend the subject so that he would be unwilling to continue the interview.

20. Subject responds positively to some statements with "no" instead of "yes".

It is very important that you understand the subject's responses. Therefore, you can stop at any time and explain that you are confused and want to be certain you understand. If it turns out that the subject is responding "no" (meaning "yes") to a negatively phrased statement, ask that he respond "true" so that you won't be confused by the answer. If it turns out that the subject is simply saying"no", then you may want to emphasize that he need only respond to the statements that he is sure describe him.

24. When to code "9".

1. Subject refuses to answer a statement.
2. Subject doesn't understand a word or an entire statement and is unable to answer.

DO NOT CODE "9" when a subject is simply not sure whether or not the statement applies to him. Repeating the introductory statement for that category may help him decide whether the statement describes him. If he is still uncertain, leave that statement blank and go on with the interview.

21. Subject with a variable illness says that today is a particularly good day or a particularly bad day and has difficulty answering.

Explain that you understand his state of health may vary but that the questionnaire is designed to measure his behavior on a particular day and he should try to answer as best he can as of today.

23. Subject complains about you reading the statement at the top of every page.

Explain that for someone who obviously understands the instructions it may seem unnecessary but that many people appreciate the reminder. Since all the interviews need to be done in a standard way, you are have been instructed to read it every time.

23
24. Subject is not sure how to respond to a statement because he is able to do the activity but still doesn't do it.

Explain that the questionnaire is not meant to measure what a person is able to do but rather his actual behavior, in other words, what he is actually doing or not doing. Therefore, we are interested in whether he is sure this statement describes his behavior today and is related to his state of health.

APPENDIX L

Katz Adjustment Scale (Relative's Form)

Clinical Study of IPPB

Instructions for Administration

Preliminary to the administration of the separate inventories, the interviewer should paraphrase the following:

The forms which I shall ask you to fill out are designed to give us some idea of how (subject's name) is from day to day, his (her) behavior, and how he (she) gets along with other people. It will give us some idea of what he (she) has been doing and how well he (she) has been getting along within the past few weeks. (Note: Whenever a respondent has difficulty in understanding these oral directions, it is permissible to rephrase or explain them if the original meaning is retained.)

The following explanations should be read to the respondent:

Form R1 (Parts I & II)

"There are a number of statements on this list which describe different kinds of behavior and mood. These include symptoms that people who have been in the hospital sometimes show. Would you go through them and indicate how _____ _____ has looked to you during the past few weeks on these things. Alongside each statement are four possible answers.

"If, in your opinion, _____ is never like this, or only rarely, then place a check in the first box (1).

"If, _____ is this way sometimes, but not too frequently, place a check in box (2).

"If, _____ is like this often, check box (3).

"Place a check in box (4) if the statement would describe _____ or his (her) behavior always or practically always. For example, where the statement reads "has trouble sleeping," if _____ is sometimes bothered by this, then you would place a check in box (2). If, as far as you know, he (she) never or very rarely has any difficulties with sleeping, then you would check (1).

Do not spend too much time on any one question but make sure that you check every question."

Form R2: General Activities

"People differ in what they are able to do. I would like you to go through this list and tell me which of these things _____ is doing or has done within the past few weeks. For example, if _____ is not helping

with the household chores you would place a check in column (1). If he(she) helps some, then you would check column (2). If he (she) is doing this regularly, then place a check in column (3)."

Form R3: Expentations (BASELINE ONLY)

"Families differ in what they think their relatives should do. Now let's go back over the list. I want you to tell me which of these things you expect _____ will be doing after he (she) has been in this study for a month. For example, if you expect _____ to be regularly helping with the household chores, then place a check alongside the statement in column (3). If you do not expect him (her) to be doing any of this, then place the check in column (1)."

Form R3: Expectations (Other than BASELINE)

"Families differ in what they think their relatives should do. Now let's go back over the list. I want you to tell me which of these things you expected _____ to be doing. For example, if you expected _____ _____ to be regularly helping with the household chores, then place a check alongside the statement in column (3). If you didn't expect him (her) to be doing any of this, then place the check in column (1)."

Form RS4: Free-Time Activities

"What does _____ do with his (her) free time? I want you to go through this list and tell me which of these things he (she) is now doing. For example, if he (she) frequently works in and around the house, place a check in column (1). If he (she) does this sometimes, check column (2). If he (she) never, or almost never does it, place a check in column (3). Be sure and put a check in one of the columns after each item."

R5: Satisfaction with Free-Time Activities

"Are you satisfied with the way _____ spends his (her) free time? Let's go through the list again and this time indicate whether you would like to see him (her) doing more or less of these things."

(When the relative returns the form, check to see whether all items have been completed.)

NIH IPPB STUDY

AERO-TEST EQUIPMENT CULTURE PROTOCOL

1. Instruct patient to assemble his equipment as he would routinely do to begin a treatment. Patient should add his liquid bronchodilator to the nebulizer as usual.

2. Attach nebulizer to bracket at side of machine after patient has prepared equipment for treatment.

3. Remove the Aero-Test from the bag and set the Aero-Test unit near the equipment to be cultured. NOTE: Handle the Aero-Test with care to avoid accidental contamination.

4. Remove the mouthpiece from the manifold. Add a five inch piece of flex tubing in place of the mouthpiece.

5. Remove the lid from the sterile Aero-Test. (Figure 1).

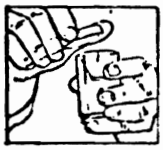

Fig. 1

Place the lid upright on a flat surface.

6. Turn the machine to the 'on' position.

7. Allow machines to be 'on' for 10 seconds before collecting sample.

8. With the equipment running, insert the end of the flex tubing firmly into the Aero-Test funnel end. (Figure 2).

Fig. 2

Sampling time for both types of equipment should be 2 minutes.

9. Immediately following the collection of the sample, separate the culture plate from the Aero-Test cylinder. (Figure 3).

Fig. 3

Discard the cylinder and place the lid over the culture plate. (Figure 4).

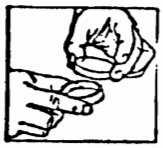

Fig. 4

NOTE: To avoid extraneous contamination, do not reopen the culture plate of a sealed, completed sample. Tape the lid to the plate.

10. Turn the culture plate over and label the specimen with the date and time of culture as well as the patient's name and identification number.

11. During transport of the specimen to the laboratory, the culture should be protected from extreme heat or cold.

12. The specimen should be delivered to the laboratory for evaluation within 4 hours of the collection time.

13. In the laboratory the Aero-Test culture plates should be incubated for 24 and 48 hours at 35-37 degrees Centigrade. At the end of the 24 and 48 hour periods, count the number of colonies. Growth on the plate is interpreted as follows: (Figure 5)

Colony Count	24 Hours	48 Hours
0-5	contamination unlikely, but incubate additional 24 hours.	no contamination
6-40	suspect contamination	suspect contamination
40+	suspect heavy contamination	suspect heavy contamination

14. Sub-culture colonies in accordance with an appropriate reliable technique such as that described in the Manual of Clinical Microbiology edited by Edwin Lennette, Earle H. Spaulding and Joseph P. Truant, or Bailey and Scott's Diagnostic Microbiology. (see accompanying bibliography).

Procedure revised by Loma Linda University Medical Center Respiratory Care Department on December 18, 1978.

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APPENDIX N

THE BENNETT IPPB/CN PERFORMANCE TESTER

INTRODUCTION:

The Performance Tester is used to determine if either the Bennett IPPB device or the Bennett Compressor Nebulizer are working properly. In the IPPB test, it will indicate flow and pressure values. In the Compressor Nebulizer test, it measures pressure.

Pressure against the nebulizer jet can be measured with the pressure gauge (small gauge) to indicate nebulizer jet obstruction, relief valve adjustment, and compressor output.

The flow gauge (large gauge) measures back pressure against a fixed orifice (Flow Adaptor) to indicate flow values. A decrease in flow output would indicate a clogged venturi filter or jet, a bad regulator, or a malfunctioning Bennett Valve.

The Performance Tester is a fragile piece of equipment and is calibrated to read horizontally with the gauges facing up. The flow gauge should read zero with no flow and has been calibrated for use with the Flow Adaptor provided with each unit. Both tester and Flow Adaptor are coded with matching identification numbers.

PERATION:

Connecting the Performance Tester - Compressor Nebulizer:

Attach the short section of hose on the pressure gauge tee to the Bennett Nebulizer output nipple on the face of the machine. Attach the nebulizer drive line to the end of the tee. You are now ready to test the unit.

Connecting the Performance Tester - IPPB:

Attach the short section of hose on the pressure gauge tee to the Bennett Nebulizer output nipple on the face of the machine. Attach the nebulizer drive line to the end of the tee. Attach the patient circuit to the face of the IPPB Device. Attach the Flow Adaptor to the mouthpiece end of the manifold. You are now ready to test the unit.

Pressure Measurement (Compressor Nebulizer and IPPB):

Fill the medication vial with 4cc distilled water and turn the unit on. Note if mist is present coming from the nebulizer. The pressure gauge should be in the range of 6.0 $\pm$ 0.5 psi. If the readings are within these limits, the Compressor Nebulizer is ready for patient usage.

If a mist is not present or nebulizer pressures are incorrect, replace the nebulizer jet and check all connections for leaks. If this does not solve the problem, the unit should be brought in to be serviced.

Flow Test - IPPB:

All distilled water and moisture should be removed from the nebulizer before making this test. The pressure regulating knob should be turned fully clockwise and the unit turned on. Initiate the inspiratory phase by lifting up on the Bennett Valve. At these settings the Bennett Valve should turn off at 28 to 35 cm H_2O when flow is gradually occluded. Turn on the Bennett Valve again and observe the amount of back pressure registered on the flow gauge. The amount of flow can be read from the graph provided for the specific tester being used. Accurate readings depend on a leak free circuit, horizontal zeroing and reading of the gauge, and positioning of the flow adaptor so that nothing obstructs the flow passing through it.

Maximum flow should be greater than 70 lpm which corresponds to a back pressure of 6 cm H_2O. If the flow is less than 70 lpm, clean the Bennett Valve and observe that its vertical movement is not hampered as inspiration is initiated. If the flow valve is still less than 70 lpm or the shut off pressure is not in the 28-35 cm H_2O range, the unit should be brought in for service.

Operative Check - IPPB:

Remove the flow adaptor and attach a test lung to the patient circuit. Turn on the unit and cycle it with the test lung. Check to see if the Bennett Valve "turn on" sensitivity is - 1.5 ± 0.5 cm H_2O. If the unit does not meet these specifications, clean the Bennett Valve thoroughly and retest. The unit should be serviced if it still does not meet the sensitivity specifications.

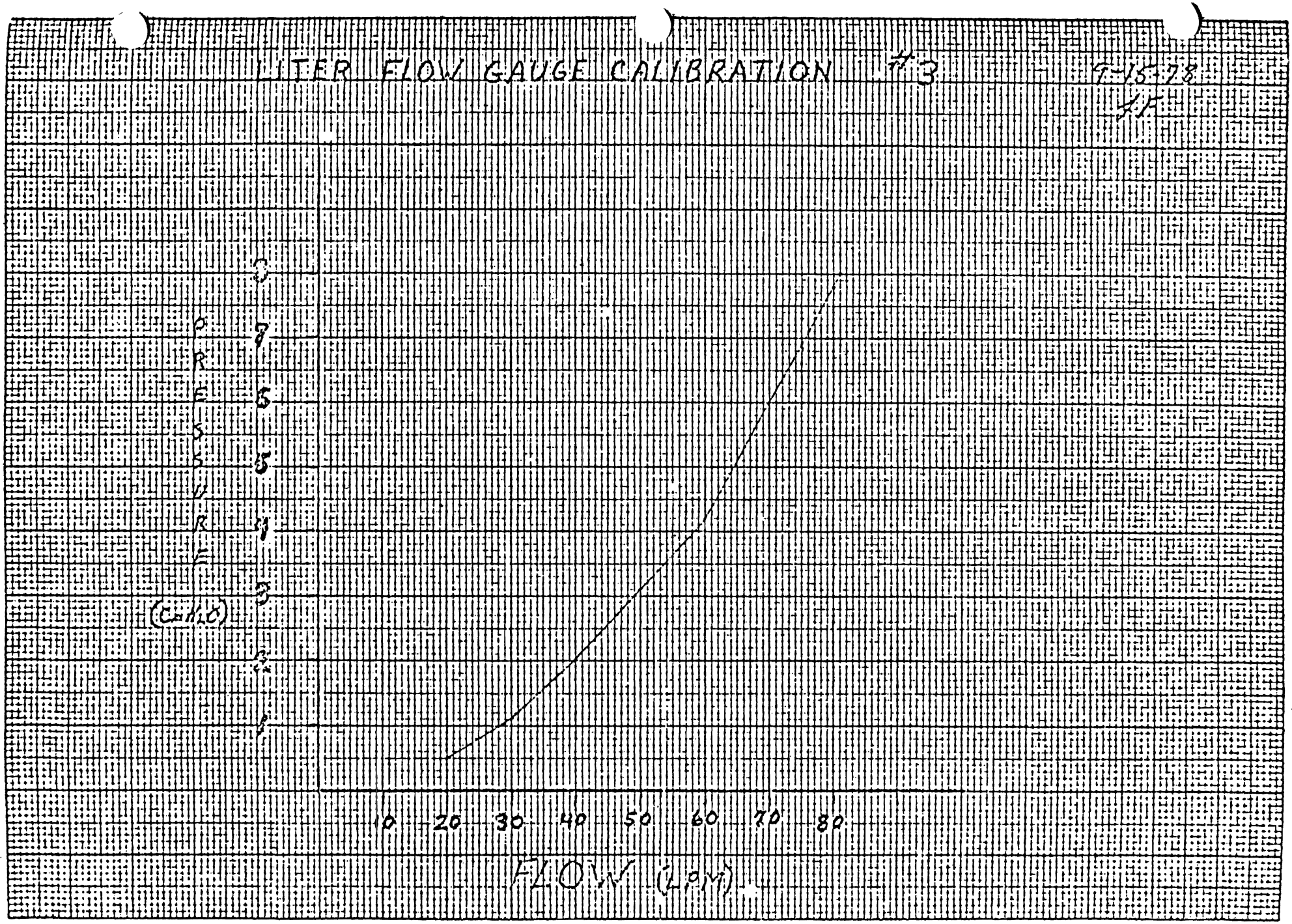
Using the test lung, adjust the IPPB device to the pressure prescribed for the patient. The unit is now ready for patient usage.

PREVENTIVE MAINTENANCE:

The Bennett Compressor Nebulizer and IPPB device should receive preventive maintenance every 1,000 hours of running time or each six months which ever occurs first. Units that are used in or around dusty or dirty conditions may require preventive maintenance more frequently.

The Bennett IPPB/CN Performance Tester should be recalibrated semi-annually against an accurate air rotometer.

Questions regarding use of the tester can be directed to Bio-Medical Services for the Department of Respiratory Care, Loma Linda University Medical Center, Loma Linda, CA., phone 714-796-7311, ext. 3046.



APPENDIX N (Continued)

APPENDIX O

NIH IPPB STUDY

Protocol For Measuring Expired Tidal Volume
With The Bourns Ventilation Monitor LS-75

Equipment needed:

Bourns Ventilation Monitor LS-75
Bennett Gas Collector Head, Bennett Part # 5540

Procedure:

1. Remove the Exhalation Diaphragm (Part # 8950, 3248, and 0723) from the patient's nebulizer (Part # 2664). (Figure 1)

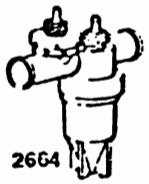


Figure 1

2. Attach the Bennett Gas Collector Head, (Figure 2), to the nebulizer, (Figure 3).

Figure 2

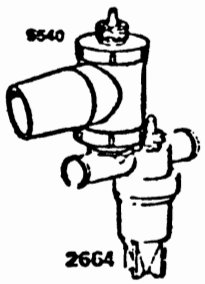


Figure 3

3. Insert the Universal Adaptor (Part # P/N 50000-01004) into the Gas Collector port. (Figure 4)

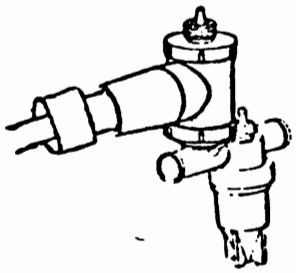


Figure 4

4. Attach the Ventilation Monitor Flow Tube (Part # P/N 50000-00075) to the Universal Adaptor (Part # P/N 50000-01004).

5. Have the patient initiate an inspiration and observe his rate and pattern of ventilation to insure he is using the correct procedure.

6. During the inspiratory phase of a breathing cycle, activate the ventilation monitor by pressing the "Spont" mode. Count the patient's respirations for one minute.

7. At the end of the minute, observe the minute volume in liters and the respiratory rate which will be displayed on the monitor.

8. To determine the patient's actual tidal volume, subtract 4 liters from the minute volume displayed on the ventilation monitor, and divide by the respiratory rate for one minute.

9. Repeat this procedure again and record the results of the second trial.

APPENDIX P

EXAMINATION OF LUNGS OF SUBJECTS DYING IN IPPB STUDY

A. General Policy

It is estimated that approximately 130 patients will die during the course of the study. Every attempt should be made to obtain autopsy permission. Next of kin should also be instructed to notify the principal investigator as soon as possible of the death of a study patient. Some of these patients may qualify as coroner or medical examiner cases and an attempt should be made to secure an autopsy at the participating institution. If unsuccessful, one of the institution's pathologists should be present at the coroner's autopsy. The coroner should be advised of the study and given a copy of the protocol in advance in order to enhance his cooperation.

B. Examination of Lung

(1) The lungs and heart of patients registered in the University of Manitoba study will be studied at the Health Sciences Centre, Winnipeg. Lungs and hearts of patients dying in the United Stages will be shipped to Denver, Colorado for processing. They should be transported as soon after the necropsy as possible, preferably within one hour of the completion of the case.

(2) Recompense for Inconvenience and Transport of Lungs to Airport. We recognize that fulfillments of the requirements of this protocol entails extra work for various individuals in the Pathology Departments concerned. Therefore, arrangements will be made to recompense individuals involved and the amount and method will be arranged through Dr. Lynn Blake's office.

C. Autopsy Procedures

(1) The heart and at least one lung should be removed from the thorax.

(2) One unopened lung, preferably the left, with the bronchus left long (cut flush with the tracheal carina) will be wrapped in plastic, e.g. Saran wrap) and stored at 4°C until shipping.

(3) Following whatever pathological examination is required by the controlling pathologists, including dissection and tissue sampling, the remaining heart will be wrapped in plastic sheeting and stored at about 4°C until shipping. The weight and sites of all tissue removed should be recorded and forwarded to the NOTT & IPPB Pathology Centre, c/o Dr. Thomas L. Petty, Webb Waring Institute, 4200 East Ninth Avenue, Denver, Colorado 80220.

(4) The following information should be sent to the Denver Centre:

Patient's Name _____ Date of Birth _____

Study Identification Number _____ Autopsy Number _____

Body Length _____

Time of Death _____ Time & Date of Autopsy _____

Weight of heart tissue removed (state from where) _____

A copy of the final autopsy protocol should be sent to:
Dr. William M. Thurlbeck, Department of Pathology, Health Sciences Centre, 700 William, Winnipeg, Manitoba R3E 0Z3, Canada.

D. Shipping Instructions

The undissected lung and the heart should be placed in an insulated shipping container. These can be obtained from various sources. The cheapest source is from a pet store where insulated containers are used for shipping tropical fish to the pet store. These can usually be obtained for a nominal sum of money or for no money at all. Alternatively, insulated mailers may be obtained from the Horizon Ecology Company, 7435 North Oak Park Avenue, Chicago, Illinois, 60648, catalogue #3732 (These cost $9.00 each or 6 for $48.60). Other insulated containers are, of course, equally suitable. 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 about at 4°C and not freeze them. The box should be wrapped in paper and marked FRESH BIOLOGICAL SPECIMENS: RUSH: THIS WAY UP. The container should then be taken to the small parcels office of the appropriate airline or may be shipped air freight. When the package has been received by the airline and flight number known, the participatory organization should phone Dr. Tom Petty (area code 303, 394-7767). After hours, in case of emergency, or if no response is available at the above number, phone the hospital operator (area code 303, 399-1211) and ask for Wayne Silvers page boy number 324. He can be reached on a 24 hour basis.

The package should be addressed to:

NOTT & IPPB Pathology Centre
c/o Dr. Thomas L. Petty
Webb Waring Institute
4200 East Ninth Avenue
Denver, Colorado 80220
U.S.A.

APPENDIX Q

THEOPHYLLINE CODE LIST

01	Theo-Dur
02	Sustaire
03	Slo-Phyllin
04	Theobid
05	Airet L.A.
06	Elixophylline-S.R.
07	Theophyl SR
10	Theophylline
11	Aminophylline
12	Choledyl
13	Tedral
14	Theolair
15	Quibron
16	Elixophyllin
17	Marax
18	Acet Aminophylline
19	Bronkodyl
20	Other