HIGH FREQUENCY VENTILATION (HIFI) TRIAL

Manual of Operations

October 1, 1987

PREFACE

This manual is concerned solely with the collection of the data specified in the study protocol. Procedures to be followed in systematically collecting and recording study data are discussed in this manual. The design of the study is discussed in the Study Protocol.

All personnel who are involved in this study are urged to read this manual and the study protocol very carefully. Questions about the operational aspects of the study protocol and the procedures discussed here should be discussed with the Principal Investigator/Co-Investigator.

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LIST OF EXHIBITS

I. INTRODUCTION

The High Frequency Ventilation Trial (HIFI) is sponsored by the National Heart, Lung and Blood Diseases Institute. The objective of the study is to assess the efficacy and safety of High Frequency Ventilation (HFV) relative to Conventional Mechanical Ventilation (CMV) in infants. Eligible infants will be enrolled in the study by fourteen clinical centers.

All infants, inborn or transported to the study hospital, up to 24 hours of age and with birthweights between 750 and 2000 grams, will be screened for the study if they require oxygen or assisted ventilation. Those who are determined to be eligible should be enrolled in the study after a legal guardian or a parent signs an informed consent agreement. The infant will be assigned to HFV or CMV following the procedures discussed later in this manual.

Infants enrolled in the study will be carefully monitored during their hospitalization. A considerable amount of data will be gathered on the infants. These data will be entered on data collection forms designed for this purpose. Completed data forms (originals) should be promptly shipped to the Coordinating Center for processing and statistical analysis. Copies should be kept at the originating clinic.

The procedures that should be followed in this study are discussed in the sections which follow.

II. PATIENT ENROLLMENT

A. Who Are Eligible to Enter the Study?

All inborn and transported infants with birthweights between 750 and 2000 grams and up to 24 hours of age will be candidates for the study if:

1) They have respiratory distress with respiratory failure, including HMD, pneumonia, persistent pulmonary hypertension, etc. ("respiratory failure" is defined loosely to include hypercapnia, hypoxemia requiring supplemental O_2 and apnea or abnormally low respiratory frequency), and
2) They are in need of assisted ventilation.

In order to qualify for the study, the infant should meet the following additional criteria under the circumstances described below:

1) For infants weighing in the 750-1250 gram range, the need for assisted ventilation is the only qualifying criteria.
2) For infants weighing in the 1251-2000 gram range, the qualifying criteria is based on a $P_aO_2/F_IO_2 < 100$ and receiving CMV at a Paw of >=9 cm of H_2O. This criteria must be confirmed by two consecutive blood gas determinations at least 30 minutes apart and not more than 90 minutes prior to the initiation of the randomly assigned mode of therapy.
3) If the infant was treated with CMV prior to qualifying for the study, the duration of CMV treatment does not exceed 12 hours.

Infants who have any one of the following should be excluded:

1) meconium aspiration,
2) neuromuscular conditions affecting respiration (e.g., major CNS malformation or pathology),

3) hydrops fetalis,

4) congenital heart disease except PDA, and asymptomatic atrial or ventricular septal defects,

5) major congenital malformations, e.g., chromosomal, diaphragmatic hernia, hypoplastic lung (Potter-like syndrome), gastrointestinal,

6) multiple births of three or more,

7) infant judged nonviable by the center PI.

B. Informed Consent

The consent of the parent or legal guardian is absolutely essential for the infant to enter the study. An informed consent form describing the study has been prepared for this purpose by each center. Personnel who screen infants for the study should explain the study to the parent/legal guardian and obtain consent in the form of a signature on the Informed Consent Form. Infants whose parents/guardians refuse consent shall not be entered into the study.

C. Random Assignment of a Mode of Ventilation to Study Infants

Each qualified infant for whom the parents/guardians have granted permission to participate in the study will be assigned to one of the two modes of ventilation: CMV or HFV. The following procedure should be followed to ensure that the assignment is random within hospital and within four birthweight groups defined by 250 gm increments between 750 gm and 1500 gm (750-1000, 1001-1250, 1251-1500) and a single stratum for infants between 1501 and 2000 gm:

(1) A Screening Form will be initiated on all infants who are candidates for the study. A study ID number will be assigned to each infant at the clinical center in the order in which they are screened. The screening forms will be filled out as completely as needed and will be forwarded to RTI.

(2) RTI will supply a set of sealed envelopes in a box for each birthweight stratum. Each envelope will contain the treatment assignment for a patient. This set of envelopes will have sequentially assigned numbers on the outside to permit them to be taken in order, and to permit them to be properly reordered in case accidental shuffling occurs. In addition, each envelope will have a center code and a strata identification number in the right hand corner to further assist in avoiding any mishaps. For example, all envelopes at Case Western Reserve will have 05 plus a 1, 2, 3, or 4 in the upper right corner. The 1 will be for the first stratum, 750-1000 gram babies; the 2, 3, and 4 for the subsequent strata. These envelopes will be used for infants who qualify for the study and will be opened only after agreement to participate in the study has been obtained. The label should be affixed to the bottom of the last page of the screening form.

(3) The envelopes in each strata will be sequentially assigned to infants in that strata. If a twin pair qualifies, they both will be assigned to the same treatment -- the treatment assigned to the first born twin.

(4) The Coordinating Center will monitor the adherence to the assignment system by using the sequence number, date, and time of screening.

(5) The Principal Investigator will assume responsibility for the integrity of the screening and randomization system. Any cases of violation of the system (for example, not enrolling the patient after finding out which ventilator the patient would be assigned to) will be closely monitored by the PI, must be made known to the Coordinating Center, and the treatment assignment envelopes for all such cases should be returned to the Coordinating Center with relevant information.

III. PATIENT IDENTIFICATION NUMBERS AND RELATED COMPUTER GENERATED LABELS

Computer generated labels needed for the data collection forms will be supplied by the Coordinating Center.

A. Identification Numbers

Every infant screened in this study from each of the fourteen centers will have a unique eight-digit study identification number. The first two digits will be a center identification number. The next four digits will be a sequence number for the family within the institution. In general, these numbers will be in the ascending order in which infants are enrolled in the study. However, certain combinations of digits have been eliminated because they present problems in checking certain types of keying errors. In the case of twins, these four digits will be the same for both.

The next digit will be one (1) for a single infant and for the first born twin, or (2) two for the second born twin.

The last digit, the eighth in the identification number, is a check digit. The sole purpose of the check digit is to aid the Coordinating Center in checking for keying/transcription errors in the ID number.

The center identification numbers are as follows:

Center	ID No.
St. Margarets Hospital, Boston	02
New England Medical Center, Boston	03
University of California, San Diego	04
Case Western Reserve, Cleveland	05
Womens Hospital, Manitoba	06
St. Boniface Hospital, Manitoba	07
University of Miami, Miami	08
Pennsylvania Hospital, Philadelphia	10
Children's Hospital, Philadelphia	11
Hospital for Sick Children, Toronto	12
Mt. Sinai Hospital, Toronto	13
Vanderbilt University, Nashville	14
University of Washington, Seattle	15
University of Wisconsin, Madison	16

As an example of this scheme, the very first infant screened at St. Margarets Hospital will have an ID Number of 0200011 plus the check digit. There may be an occasion when an infant is considered ineligible for enrollment when they are first screened but circumstances change (perhaps a parent reconsidered giving consent) and the infant is deemed eligible. That infant should have a second screening form completed and the same ID number should be used on that screening form as well as all subsequent forms.

B. Computer Generated Labels

The computer generated labels will be organized on sheets and may be peeled off to be used as needed. The labels needed for an infant and its twin will be grouped together as a set. These labels are for use in the following contexts:

- to affix on each of the forms,
- for the patient log and infant's hospital record.

Each set of study ID labels will have 12 labels with 1 as the seventh digit and 12 labels with 2 as the seventh digit in the event a twin is enrolled. (Only one maternal and perinatal form need be completed for a set of twins.

The Study ID for the first twin should be affixed on this form.) The exact number of labels per ID may be changed if needed.

IV. SCREENING AND ENROLLMENT

All inborn and transported infants of appropriate birthweight and age should be screened for the study. The screening process will generally involve the following sequence of steps:

1) Assign ID number to the infant, affix it to the form.

2) Initiate a screening form.

3) Determine whether the infant is disqualified on an exclusion criterion.

4) If the infant is not disqualified on the basis of exclusion criteria, determine whether the infant meets the appropriate blood gas or need for assisted ventilation criteria and other qualifying criteria.

5) Be certain that both a high frequency ventilator and a conventional ventilator are available. If they are and the infant is qualified, seek agreement for participation in the study.

6) If an agreement for infant's participation in the study is secured, proceed as follows:

   a) Open the next "Randomization Envelope" for the appropriate birthweight stratum. Affix the randomization label to the bottom of the last page of the screening form.

NOTE:

The assignment of ventilator given in a randomization envelope is meant for the infant for whom the envelope was opened. If the infant is not initiated on the assigned ventilator, that assignment should not be used for another qualified infant. The randomization label should be affixed whether or not the infant is in fact initiated on the assigned ventilator.

This completes the enrollment process. The Screening Form must be completed to the extent required and promptly mailed to the Coordinating Center.

Each center must maintain its own log or must have access to a log of all inborn and transported infants. Such a log will help study personnel identify potential study infants as well as ensure that all candidates are screened for the study. A log of infants who are candidates for the study with the following information will be useful in this context: Infant's name, Hospital number, and Study ID number.

Remarks on Enrollment of Twins

If a twin pair qualifies, they both should be assigned to the same treatment. The randomization envelope appropriate for the weight of the first born twin should determine the treatment to be assigned to the infant.

V. DATA COLLECTION

A. Data Forms

The data which will be collected on infants enrolled in the study will fall into the following broad groups:

- socioeconomic data on infant's family;
- maternal pre-pregnancy and pregnancy history;
- labor and delivery data;
- fetal and perinatal data;
- detailed evaluation of infant's course in hospital; and
- follow-up evaluations.

The data will be collected using the following standardized data collection forms:

1. Screening Form
2. Maternal and Perinatal Data Form
3. Infant Entry and Hospital Form
4. Flow Data Form
5. Cross-Over Form
6. Protocol Interruption Form
7. Termination Form
8. Follow-Up Forms.

The copies of the forms will be supplied by the Coordinating Center.

B. Schedule for Completion of Forms

The Screening Form must be completed on all infants who are candidates for the study. Other data forms should be completed only on infants who are randomized (including those who were withdrawn prior to being initiated on the assigned ventilator).

A Maternal and Perinatal Data Form should be filled out on every single infant. In the case of twins, only one need be completed using the ID of the first born twin.

A Flow Data Form and an Infant Entry and Hospital Form should be completed on every randomized infant. The data should be recorded as they are

collected during the entire course of the infant's stay in the hospital. The completed form should be mailed to the Coordinating Center after the infant is discharged to home or expires.

A Cross-Over Form should be completed every time a randomized infant meets crossover criteria whether or not that baby is actually switched from one mode of ventilation to the other. Therefore, in some instances, more than one cross-over form may be completed on an infant. A form should also be filled out if a baby is switched without meeting criteria.

A Protocol Interruption Form is to be completed whenever the ventilatory support (protocol) is interrupted for an hour or more. It may be necessary to complete this form more than once on some infants.

A Termination Form is to be completed if the infant (1) is terminated from the study, (2) is lost to follow-up during the follow-up period, or (3) dies.

An Autopsy Form should be completed whenever a postmortem is performed.

VI. GENERAL INSTRUCTIONS ON DATA COLLECTION

A. Instructions on Recording Data

1. Complete all forms legibly using blue or black pen or a pencil or a typewriter. Do not use a red or green pen or pencil as red and green are used to edit the forms. All names and words other than the signatures of the clinical center coordinators and examiners should be printed or typed one letter per box. A blank space should be left between each word. Numbers should also be clearly written or typed with one number per box.

2. Identifying Information. The identifying information on the forms will always include the infant's identification number (ID) so that all the forms relating to a particular infant can be linked together. Therefore, care must be taken to ensure that the identification information and the data on each form are related to the same baby.

   A supply of self-sticking labels will be provided for use in identification of the various forms.

3. Date of Birth. Several forms have a question asking the date of birth of the infant. Numbers should be right justified and leading 0's should be used to record months or day of one digit.

	Month	Day	Year
Correct:	0 5	0 1	8 6
Incorrect:	5	1	8 6
	(no leading 0's)		
Incorrect:	5	1	8 6
	(not right justified)		

4. When the time of day is requested as a part of an answer to a question, give the answer in military time units. For example, 1:15 a.m. would be recorded

0	1	1	5

while 1:15 p.m. would be recorded as

1	3	1	5

.

5. To record the answers to multiple choice type questions, place a check (√) in the box to the right of the appropriate answer. For example, when answering a yes or no question such as:

	Yes	No
Ventilator available?		

it should be recorded as follows:

	Yes	No
Correct:	√	
Incorrect:	x	

6. As with dates, numbers should be recorded using leading 0's when necessary and should also have 0's in the tenths and hundredths column as necessary. All numbers should be right justified. For example, a blood pressure reading of 99 would be correctly and incorrectly recorded as follows:

Correct: | 0 | 9 | 9 |

Incorrect: | | 9 | 9 | (no leading or trailing 0's)

Incorrect: | 9 | 9 | | (not right justified)

Always record numbers with just digits rather than with digits and fractions. Always use the indicated units when measurements are requested and make sure the decimal is in the correct place. For example, when recording a length in cm, record as follows:

Correct: | 4 | 0 | . | 0 | cm.

Incorrect: | 4 | 0 | . | | cm.

7. Print the entries you place on the lines marked "specify". These must be read and coded by people who do not necessarily have a medical background.

B. Mailing Completed Forms

Data collection forms should be completed in a timely manner, reviewed and signed by an authorized person at the clinical center, and the originals sent to the Research Triangle Institute as quickly as possible. It is important to use a sturdy mailing envelope to ensure that data forms are not damaged in transit. Address labels for mailing envelopes will be provided. They will read as follows:

The Research Triangle Institute
ATTN: Judith Katzin - Project 3011
Post Office Box 12194
Research Triangle Park, NC 27709-2194

VII. INSTRUCTIONS FOR COMPLETING FORMS

This chapter provides detailed instructions on collecting and recording data on each study form. Each subsection of this chapter discusses a form. Topics covered include the following:

- how often and when a form is to be completed;
- operational definitions of data items.

Each data item (question) on the form is followed by instructions on recording data.

A. Screening Form

The Screening Form must be completed on all inborn and transported infants who satisfy the following criteria:

1. birthweight between 750 and 2000 grams (includes 750 grams and 2000 grams);
2. 24-hours of age or younger; and
3. require oxygen or assisted ventilation.

More than one screening form may be completed on an infant and it's unique ID should be used for any subsequent screenings. Questions 1 through 9 should be completed on every Screening Form.

Background Information:

1. INFANT ID:

   Affix the ID number label.

2. DATE AND TIME OF BIRTH:

   Record month, day, year. Use leading zeros. For example, February 8, 1986 is recorded as 020886. Use a 24-hour clock (midnight = 2400 hours; 1 minute after midnight = 0001).

3. DATE AND TIME OF SCREENING:

   Self-explanatory.

4. BIRTH WEIGHT:

   Record birthweight in grams.

   Inborn: weight on admission to NICU
   Outborn: weight at birth; if not known, weight on admission to NICU

5. INFANT DATA:

   Best estimate for gestational age as judged by Dubowitz, Ballard, Modified Dubowitz.

6. PRELIMINARY DIAGNOSIS (check all that apply):

A. APNEA (primary or secondary):

Respiratory pauses lasting >15 sec. requiring intervention. Recurrent apnea of prematurity requiring treatment with either aminophylline or nasal CPAP.

B. PNEUMONIA:

Infection of the lower respiratory tract defined by the following characteristics:

When present at or shortly after birth, pneumonia will be defined by the presence of all of the following:

1) clinical signs of respiratory distress (tachypnea, grunting, retractions, cyanosis);

2) improvement in arterial PO_2 with supplemental oxygen;

3) chest radiographic evidence of focal pulmonary consolidation or diffuse lung densities;

4) indirect evidence of infection (i.e., maternal/neonatal infection, fever, neutropenia, etc.)

C. RESPIRATORY DISTRESS SYNDROME:

The diagnosis of respiratory distress syndrome or hyaline membrane disease requires the following.

1) prematurity; < 37 weeks gestation;

2) respiratory distress not attributable to other causes unless more than one diagnosis is marked (e.g., pneumonia and RDS);

3) inspired oxygen concentration greater than 30% to maintain an arterial oxygen tension greater than 60 mm Hg beginning during the first 24 hours after birth;

4) retraction and poor air entry during spontaneous respiratory effort; and

5) chest radiographic findings of decreased lung volume, air bronchogram, diffuse, very finely or reticular infiltration persisting at least until the third post-natal day.

D. RESPIRATORY DISTRESS OTHER:

This category includes presenting respiratory distress syndromes such as transient tachypnea of the newborn, Type II respiratory distress, wet lung, pulmonary edema, etc. and other forms of respiratory distress occurring shortly after birth for which a specific diagnosis is not listed in this section.

E. DRUG RELATED DEPRESSION:

Respiratory depression related to maternal drugs administration during labor and delivery.

F. ASPHYXIA:

Clinical signs (hypotonia, apnea, seizures associated with fetal or neonatal distress, or Apgar score $\leq$ 5 at 5 minutes, or base deficit larger than 8 during first 30 minutes.

G. OTHER (specify):

H. NONE:

Self-explanatory.

7. IS THE INFANT ON IPPV?

Check the box which indicates whether the infant is on IPPV. IPPV includes mechanical ventilation or hand bagging. Time includes the sum of mechanical ventilator and hand bagging. Record hours and minutes. If duration of IPPV $>$ 12 hours, infant is excluded from study.

8. EXCLUSION DIAGNOSIS (check all that apply):

These diagnoses exclude the infant from the study.

A. MECONIUM ASPIRATION:

Meconium in amniotic fluid and/or meconium present in airway; and clinical respiratory distress and radiographic changes consistent with meconium aspiration.

B. NEUROMUSCULAR CONDITIONS AFFECTING RESPIRATION:

Includes primary muscle disorders, spinal cord or phrenic nerve injury. Primary muscle disorders, e.g., myotonic dystrophy, myasthenia gravis

C. HYDROPS FETALIS:

Hydrops from any etiology.

D. CONGENITAL HEART DISEASE:

Includes major congenital heart disease except PDA and asymptomatic ASD and VSD.

E. MAJOR CONGENITAL MALFORMATIONS:

Includes chromosomal abnormalities; dwarfism and other skeletal abnormalities affecting ventilation; hypoplastic lungs: radiographic evidence of hypoplastic lungs secondary to renal agenesis (Potters). GI malformations includes TEF, diaphragmatic hernia, gastroschisis, omphalocele or any other anomaly affecting ventilation. If in doubt, consult with PI.

F. MULTIPLE BIRTHS ≥ 3:

Self-explanatory

G. NEWBORN NON-VIABLE:

Due to severe asphyxia, extreme prematurity, overwhelming infection. If this cateogy is used, record whether infant died within 3 days.

H. NONE:

Self-explanatory.

9. ELIGIBILITY FOR THE STUDY AT THIS POINT OF SCREENING:

An infant is <u>not</u> eligible at this point if it has been on IPPV for over 12 hours, has one or more of the exclusion diagnoses, or does not

require mechanical ventilation at all. If the baby is not eligible, sign the form and mail to the Coordinating Center.

10. MOTHER'S DATE OF BIRTH:

Self-explanatory.

11. ETHNIC ORIGIN OF MOTHER:

Self-explanatory. As perceived by mother.

12. TWIN PREGNANCY:

Self-explanatory.

13. QUALIFYING DATA:

A. FOR INFANTS BETWEEN 750 AND 1250 GRAMS:
Infants may be treated with CMV for as long as 12 hours prior to qualifying. Infants weighing between 750 and 1250 grams need only require assisted ventilation to be eligible for randomization. If infant does not qualify, skip to Question 18.

B. FOR INFANTS BETWEEN 1251 AND 2000 GRAMS:
Infants in this birthweight range may also be treated with CMV for as long as 12 hours. Qualifacation for infants in the 1251-2000 gram range will be based on a $PaO2/F_IO2$ of < 100 and CMV at a $\bar{P}aw$ of ≥ 9 cm H_2O. Eligibility is based on blood gas criteria which might reasonably predict the need for mechanical ventilation to continue beyond a few hours. These qualifying criteria must be confirmed by 2 consecutive blood gas determinations at least 30 minutes apart and not more than 90 minutes prior to randomization and treatment. Skip to Question 18 if the baby does not qualify.

14. BLOOD GASES:

(enter only if the infant meets blood gas criteria for entry, i.e., both parts of Q.13.B are yes)

Record the measurements for blood gases if that criteria has been met for larger infants (both parts of 13B checked YES).

15. INFANT INVOLVED IN CONFLICTING PROTOCOL(S)?

Other Protocols: Check the box that indicates whether infant is involved with a conflicting protocol. These studies will be determined from a list of protocols at each center and reviewed by the ancillary studies committee. If YES, skip to Question 18.

16. VENTILATORS AVAILABLE?

If either is unavailable, skip to Question 18.

17. AGREED TO PARTICIPATE IN STUDY?

If agreement is not given, check all appropriate boxes and specify "other" reasons, e.g., parents or guardian unavailable.

18. DISPOSITION OF INFANT:

Self-explanatory. Specify reason for exclusion.

19. VENTILATOR ASSIGNED:

Self-explanatory.

A. DATE AND TIME OF RANDOM ASSIGNMENT

Record date and time of ventilator assignment. Time is when randomization occurs (when card is pulled). Affix the randomization label to the bottom of the Screening Form on the last page.

20. WAS PATIENT WITHDRAWN PRIOR TO INITIATION OF STUDY VENTILATOR/PROTOCOL?

After ventilator assignment, if infant withdrawn, specify reason, (e.g., death).

SIGNATURE OF CLINICAL COORDINATOR

RECORD DATE FORM COMPLETED.

B. Maternal and Perinatal Form

A Maternal and Perinatal Form must be completed for every single randomized infant in the study. Only one form should be completed if both infants of a twin set are enrolled in the study. In this case, affix the study ID label of the first born twin on the form.

1. INFANT'S ID NUMBER:

   Affix the infant's study ID label.

2. MOTHER'S DATE OF BIRTH:

   Record month, day and year of mother's birth using leading zeros. For example, February 8, 1986 is recorded as 020886. It is important to have this information on outborn as well as inborn babies.

3.,4.,5. SES DATA:

   These three questions to establish social strata are derived from the Hollingshead Index of socio-economic status. Responses to these questions are weighted and used to derive a numerical score to place families in one of five social-strata categories. Assignment of numerical score will be done by RTI and therefore checking only the appropriate response is required on the data form.

   Questions 5A.1, 2, 3; 5B.1, 2, 3, and 4 are meant to assist you in classifying the family's occupational level. RTI will code only Questions 5A.3 and 5B.1.

   To classify the occupational level in each family, each parent's current (or last if currently unemployed) occupation is to be rated on a 6-point scale. The interviewer must be certain to get enough information to be able to make the rating. Two problems are likely to be encountered. The first is that there will be many occupations that are

not included in the examples. The second is that the label offered by the parent may be an euphemism for a very different type of work than one expects. The title "engineer" is classic; an engineer may actually be somewhere between an aerospace scientist and a building attendant or janitor.

The rating scale has four general principles. First of all, it is a rating of occupational prestige which is not intended to be synonymous with income and education background. Second, there is a basic division between "white collar" and "blue collar". This is a controversial issue, and there is evidence that the distinction is becoming less valid. (Certainly it is not valid as far as income is concerned.) Nonetheless, as a measure of occupational prestige it still appears sufficiently relevant for use in the scale. Third, a component of prestige is how much responsibility a person has. Underlings are rated lower than supervisors; self-employed generally score higher than a person doing rather similar work under another's supervision. Fourth, the scale reflects how much training or education is required for entry into the position. A "factory worker" could not be rated unless the interviewer had a sense of how long the person had to be trained to attain that position. If a person is a full-time student, score the occupation that he or she is preparing for and enter "student" and grade level in row number 7 (other). If a person is retired, score the primary occupation the person attained and enter "retired" in row 7. Unemployment is covered in item 5A.3.

Examples of the six points on the Occupational Rating Scale appear below:

Rating

1. Professional, technical, high level administrative and managerial positions.
   Examples: Accountant, architect, author, chemist, clergyman, college teacher or administrator, dentist, editor, electronic engineer, industrial engineer, lawyer, physician, government executive, officer in a business corporation, principal of a high school, statistician, business executive.

2. Managers, proprietors, "lesser" professional and technical positions.
   Examples: Banker, computer programmer, department head in a business, high school teacher, sales manager, postmaster, farm manager, salesperson in a highly technical area, high school sports instructor, director of religious education, nursing supervisor, technical photographer, administrative assistant, optician, military officer, social worker, pharmacist.

3. Sales and miscellaneous "white collar" positions.
   Examples: Insurance salesperson, real estate salesperson, cashier, bank teller, elementary school teacher, advertising clerk, clerical worker, stenographer, secretary, postal clerk, mail carrier, college student, nurse, inventory clerk, office machine operator, statistical assistant, retail salesperson, jeweler, home decorator, NCO military, social work aide, lab technician, musician.

4. "Blue collar" supervisory position, self-employed in skilled trades, crafts and trades with extensive training requirments, and higher level service workers.
   Examples: Construction foreman, shop supervisor, cabinetmaker, enlisted level military, bus operator, barber, policeman, fireman, telephone repairman, hotel bartender, tool and die worker, maitre'd, tradesman who run their own business, electronics technician, tailor, piano tuner.

5. Skilled trades at a non-supervisory level and service workers.
   Examples: Garage mechanic, carpenter, electrician, plumber, painter, paperhanger, roofer, housekeeper, waiter and waitresses, practical nurse, hospital attendant, coalminer, cement finisher, taxicab driver, animal caretaker, groundskeeper, building guard, keypunch operator, TV repairman, short order cook, operators of construction equipment, e.g., bulldozer, backhoe, etc., housewife without other employment skills, switchboard operator.

6. Semi-skilled and unskilled workers.
   Examples: Farm laborer, truck driver, apprentice level in skilled trades, janitor (sometimes called "building engineer"), assembly-line worker, stevedore, construction laborer, day laborer, parking lot attendant, messenger, bus boy.

6. Definitions for disease entities mentioned in this question are as follows:

A. DIABETES: the following scheme for classifying diabetes mellitus including diabetes apparent only during pregnancy (gestational diabetes) is provided by the National Diabetes Data Group.

Nomenclature	Old Names	Clinical Characteristics or Condition
Type I (IDDM) Insulin dependent Diabetes Mellitus	Juvenile Diabetes (JD) Juvenile-onset Diabetes (JOD) Ketosis-prone Diabetes Brittle Diabetes	Ketosis-prone. Insulin deficient due to islet cell loss. Often associated with specific HLA types with predisposition ot viral insulitis or autoimmun (islet cell antibody) phenomena. Occu at any age. Common in youth. These women are usually of normal weight but may be obese.
Type II (NIDDM) Non Insulin dependent Diabetes Mellitus	Adult-Onset Diabetes (AOD) Maturity-Onset Diabetes (MOD) Ketosis-resistent Diabetes Stable Diabetes Maturity-Onset Diabetes of Youth (MODY)	Ketosis resistant. More frequent in adults but occurs at any age. Majority are overweight. May be seen in family aggregates as an autosomal dominant genetic trait. Always requi insulin for hyperglycemia during pregnancy. Previous history of borderlin diabetes'. Impaired glucose tolerance or treatment with oral hypoglycemic agents. $HBA1_C \geq 9\% \leq 20$ weeks gestation.
Type III (GDM)[b] Gestational Diabetes	Gestational Carbohydrate tolerance	Screening Tests: All pregnant women. 50 g oral glucose load given randomly (need not be fasting). A plasma glucose 1h later ≥ 140 mg/dl or above is an indication of an OGTT.[c]
Type IV Secondary Diabetes	Conditions and syndromes associated with impaired glucose tolerance	Cystic Fibrosis. Endocrine disorders such as Acromegaly, Hyperprolactinemia Cushing's Syndrome, insulin receptor abnormalities, or aberrant forms of insulin, drugs or chemical agents, renal dialysis, organ transplantation certain genetic syndromes.

a Hollingsworth, et al., in press. Diabetes, Suppl. 2, 1985.

b All pregnant women at higher risk for gestational diabetes should b screened at the first prenatal visit. Risk factors are glycosuria, famil history of diabetes in a first degree relative, history of a stillbirth o spontaneous abortion, presence of fetal demise in a previous pregnancy, previous heavy-for-date baby, obesity in the mother, a high maternal age or parity of five or more.

c Diagnosis of gestational diabetes based on NDDG with a 100g glucose loa that two or more of the following plasma glucose excursions be met or ex ceeded: fasting 105 mg/dl (5.8 mmol1); 1 hour 190 mg/dl (10.5 mmol/l); hours 165 mg/dl (9.1 mmol/l); 3 hours 145 mg/dl (8.0 mmol/l).

B. CHRONIC HYPERTENSION:

Hypertension is defined as a diastolic blood pressure of at least 90 mm Hg or systolic pressure of at least 140 mm Hg, or a rise in the former of at least 15 mm Hg or in the latter of 30 mm Hg. The blood pressure cited must be manifest on at least two occasions six hours or more apart. Chronic hypertensive disease is defined as the presence of persistent hypertension, of whatever cause, before the twentieth week of gestation or persistent hypertension beyond six weeks post-partum.

C. Examples of other disease states of specific interest to be recorded include heart disease, renal disease, pulmonary disease including allergy/asthma, thyroid disorders, infertility, etc.

7. Pregnancy data recorded in this question should include the current delivery.

A. GRAVIDA refers to the number of times a woman has been pregnant irrespective of the pregnancy outcome. With the establishment of the first pregnancy, a woman becomes a primigravida with numbers increasing with each successive pregnancy.

B. FULL-TERM and PRE-TERM refer to total number of deliveries (living or dead). Full-term is $>$ 37 weeks, pre-term is $\leq$ 37 weeks.

C. ABORTION refers to the total number including both spontaneous and therapeutic. An abortus refers to a fetus or embryo removed or expelled from the uterus during the first half of gestation (20 weeks or less), or weighing less than 500 grams, or measuring less than 25 cm.

D. STILLBORN refers to fetal death in utero ($>$ 20 weeks or $>$ 500 gms) and no signs of life present at or after birth.

E. NEONATAL DEATHS refers to death of a live-born infant within the first 28 days post-partum.

F. Self-explanatory.

8. CIGARETTE SMOKING:

Self-explanatory.

9. ALCOHOL USE:

Self-explanatory.

10. DRUG USE:

Any use during pregnancy reported on the chart. The intent of question 10 is to assess the extent of drug abuse. Exclude therapeutic drugs except those listed.

11. Definitions for disease states mentioned in this question are as follows:

A. PREGNANCY INDUCED HYPERTENSION is the development of hypertension (as previously defined) with proteinuria, edema, or both induced by pregnancy after the 20th week of gestation.

B. GESTATIONAL DIABETES refers to documented glucose intolerance not previously evidence and now manifest during pregnancy.

C. PREVIOUS EPISODES OF PREMATURE LABOR is self-explanatory. If yes, was a beta sympathomimetic used such as ritodrine, terbutaline, etc.

D. BLEEDING refers to significant maternal bleeding occurring during the first, second, or third trimester and requiring hospitalization.

E. Self-explanatory.

12. GESTATONAL AGE:

The best obstetric estimate of gestational age at delivery regardless of method used which could be serial ultrasound, conception date, last menstrual period, and etc.

13. Total time in days and hours from rupture of membranes to delivery of infant.

14. LABOR:

Self-explanatory.

15. LENGTH OF LABOR:

Best obstetric estimate available.

16. COMPLICATIONS:

A. FEVER:

For the purposes of this study, fever will be defined as a temperature of 38.5°C.

B. ENDOMETRITIS:

The diagnosis of endometritis can be considered positive when documented in the maternal clinical chart.

17. DRUGS:

Self-explanatory.

18. STEROIDS:

Self-explanatory.

SIGNATURE OF CLINICAL COORDINATOR

RECORD DATE FORM COMPLETE

C. Infant Entry and Hospital Form

This form must be filled out on every infant randomized (whether or not initiated on assigned treatment) in the study. It should not be completed until the final disposition of the baby is known.

1. INFANT ID:

   Affix the infant's ID label.

2. DATE OF BIRTH:

   Record month, day, year using leading zeros, i.e., February 8, 1986 is written as 020886.

3. SEX:

   Self-explanatory.

4. BIRTH ORDER:

   Specify order of birth even when one of a twin pair died or remained at the referring hospital. Leave blank if single birth.

5. VENTILATOR ASSIGNED:

   Check the box which indicates type of ventilator assignment.

   A. Write the make and model of assigned ventilation.

6. DATE AND TIME OF VENTILATOR ASSIGNMENT:

   Self-explanatory.

7. COMPLICATIONS (check all that apply):

   These diagnoses should be confirmed by obstetrician at time of delivery.

   A. PLACENTA PREVIA based on obstetrical record.

   B. ABRUPTIO PLACENTA refers to an acute abruption.

   C. CORD PROLAPSE based on obstetrical record.

   D. OTHER refers to nuchal cord, anomalous insertion of cord causing hemorrhage, or other obstetrical complications.

8. FETAL LUNG MATURITY:

Check appropriate box to indicate whether test for fetal lung maturity was done on amniotic fluid obtained by amniocentesis, or from vaginal pool for patients with ruptured membranes and if so whether mature of immature, and which tests were done.

9. FETAL DISTRESS:

This is a diagnosis made by the obstetrician on the basis of continuous fetal heart rate monitoring or other documentation of significant fetal heart rate abnormality. Check the box which indicates presence of these conditions. Record lowest pH value if fetal scalp pH was measured and check box for meconium staining.

10. DELIVERY DATA:

Check type of presentation as documented by obstetrician for all deliveries, vaginal or caesarian. Check "breech" for all presentations other than vertex. Check "forceps" for all mechanically assisted deliveries including "low" forceps and vacuum extraction.

11. APGAR SCORES:

Self-explanatory.

12. RESUSCITATION:

Check YES if the infant was resuscitated in the <u>delivery room</u>. "Yes" response requires use of at least one of the 5 modalities listed under item A.

13. PHYSICAL MEASUREMENTS AT RANDOMIZATON:

Record these measurements. Use measurements made closest in time before randomization envelope is opened.

14. ULTRASOUND DATA:

A. Ultrasound at Randomization: To be completed if the infant had a cranial ultrasound just prior to or just after randomization.

B. Ultrasound After Randomization: Complete whenever an ultrasound has been done during the first seven days after randomization.

15. MAJOR DIAGNOSES:

When condition first presents itself, record date of diagnosis, code the type of ventilation infant was receiving at the time of diagnosis.

A. RESPIRATORY DISTRESS SYNDROME:

The diagnosis of respiratory distress syndrome or hyaline membrane disease requires the following.

1) prematurity;

2) respiratory distress not attributable to other causes unless more than one diagnosis is made (e.g., pneumonia and RDS);

3) inspired oxygen concentration greater than 30% to maintain an arterial oxygen tension greater than 60 mm Hg beginning during the first 24 hours after birth;

4) retraction and poor air entry during spontaneous respiratory effort; and

5) chest radiographic findings of decreased lung volume, air bronchogram, diffuse, very finely or reticular infiltration persisting at least until the third post-natal day.

B. PNEUMONIA:

Infection of the lower respiratory tract to be defined by either of the two following sets of characteristics (a or b). Check proven pneumonia if all four criteria are met. Check suspected if only the first three are met.

a) When present at or shortly after birth, pneumonia will be defined by the presence of all of the following:

1) clinical signs or respiratory distress (tachypnea, grunting, retractions, cyanosis);

2) improvement in arterial PO_2 with supplemental oxygen;

3) chest radiographic evidence of focal pulmonary consolidation or diffuse lung densities;

4) bacteriologic evidence of infection occurring at the same time, which may include either
   - a blood culture positive for a pathogen, or
   - viral cultures positive for a pathogen, or
   - evidence of antigen in blood or urine produced by a known pathogen in the neonatal period

b) When pneumonia is acquired after birth, e.g., as a complication of prolonged mechanical ventilation, the diagnosis requires the following features. Check proven pneumonia if all three are met. Check suspected if only the first two are met.

1) deterioration, in an acute (hours to one to two days) interval, in the previous clinical respiratory status which may be accompanied by fever, and

2) A simultaneous change in chest radiographic appearance which may include increased localized densities or diffusely increased densities in the lungs, and

3) indirect or direct and evidence of infection:
   - culture of the blood positive for bacterial pathogen; or
   - culture of oropharyngeal secretions positive for known viral pathogen; or
   - quantitative culture results of deep tracheal or bronchial material consistent with an infection; or
   - change in circulating white count with the development of neutropenia (less than 1000 neutrophils and bands per mm^3 or neutrophilia; presence of 25,000 or more neutrophils and bands per mm^3.

C. CONGENITAL VIRAL SYNDROME:

D. PULMONARY INTERSTITIAL EMPHYSEMA:

Radiographic evidence of interstitial air which may be unilateral or bilateral, and may be accompanied by radiographic evidence of over-distension with possible flattening of the diaphrams. Indicate side(s) involved and whether a chest tube was inserted.

E. PNEUMOTHORAX:

This is diagnosed by the presence of air in the pleural cavity separating the parietal and visceral pleura. This diagnosis can be made on clinical grounds by transillumination or by x-ray. Clinical diagnosis can be difficult except in the presence of large tension pneumothoraces. If at all possible, the diagnosis should be radiological. The definition of unilateral or bilateral pneumothoraces is self-explanatory. Recurrent pneumothorax refers to the reaccumulation of air in the same pleural space as it had occurred before. Record first two episodes and whether a chest tube was inserted.

F. PNEUMOMEDIASTINUM (RADIOLOGICAL DIAGNOSIS):

In the anteroposterior film, there will be a hyperlucent rim of air lateral to the cardiac border and thymus. Record first three episodes.

G. PNEUMOPERICARDIUM:

This is a radiologic diagnosis and is based on the finding of gas completely surrounding the heart including its inferior border. Record first three episodes.

H. PNEUMOPERITONEUM (RADIOLOGICAL DIAGNOSIS):

In the presence of pneumoperitoneum, the possibility of perforation of the bowel should always be considered. This complication of respiratory therapy is most commonly preceded by interstitial emphysema, pneumomediastinum or pneumothorax. Record first three episodes.

I. PULMONARY VENOUS AIR EMBOLISM:

This occurs when there is intravasation of gas into the circulatory system. Clinically, the infant presents with sudden catastrophic deterioration. Also gas may be withdrawn from the venous or arterial catheters. The diagnosis should be confirmed radiologically. On x-ray, gas can be seen in the systemic or pulmonary arteries and veins as well as all chambers of the heart and is particularly prominent in the hepatic veins.

J. RESPIRATORY DISTRESS-OTHER:

This category includes presenting respiratory distress syndromes such as transient tachypnea of the newborn, Type II respiratory distress, wet lung, pulmonary edema, etc. and other forms of respiratory distress occurring shortly after birth for which a specific diagnosis is not listed in this section.

K. PERSISTENT FETAL CIRCULATION/PERSISTENT PULMONARY HYPERTENSION:

This diagnosis is made in the presence of (1) evidence of right to left shunting of blood through either the patent ductus arteriosus (confirmed by a significant differential in oxygen between right radial or right temporal arterial PO_2 compared to simultaneously obtained umbilical or distal extremity arterial PO_2); or (2) evidence of right to left shunting at a patent foramen ovale as determined by echocardiographic findings.

L. BRONCHOPULMONARY DISPLASIA:

This diagnosis is made at a post-natal age of 28 days on the basis of need of supplemental oxygen on the 28th post-natal day and for more than 21 days of the first 28 days after birth, accompanied by persistent abnormal chest radiographic findings.

M. NECROTIZING TRACHEOBRONCHITIS:

Diagnosis should be based on bronchoscopy or autopsy.

N. TRACHEOSTOMY:

Self-explanatory.

O. POST EXTUBATION ATELECTASIS:

Radiographic incidence of segmental or total atelectasis occurring after extubation.

P. APNEA:

Recurrent apnea of prematurity requiring treatment with either methylxanthines or nasal CPAP.

Q. NECROTIZING ENTEROCOLITIS:

Criteria for diagnosis include abdominal distension, regurgitation, guiac positive or frankly bloody stools accompanied by a host of non-specific symptoms including unexplained recurrent apnea, lethargy, feeding intolerance, and temperature instability resulting in the patient being made NPO for more than 7 days; or radiographic documentation of pneumatosis intestinalis, portal air or free air, or surgical or autopsy evidence of necrotizing enterocolitis are necessary to establish the diagnosis.

R. JAUNDICE REQUIRING EXCHANGE TRANSFUSION:

Self-explanatory.

S. CONGENITAL HEART DISEASE:

Any structural abnormality of the heart and/or great vessels except PDA. The diagnosis must be confirmed by either echocardiography, cardiac catheterization or post-mortem examination.

T. PATENT DUCTUS ARTERIOSUS:

Symptomatic or hemodynamically significant PDA is diagnosed when cardiac or pulmonary function is compromised by left to right shunting through the ductus. This may be manifested by cardiomegaly, increased pulmonary vascularity or edema, deterioration in lung function and physical findings including murmur, bounding pulses and a hyperactive precordium. In addition, its presence may be documented by echocardiogram and Doppler flow studies. Acceptable management of this condition includes anti-congestive measures, use of oral or IV indomethacin or surgical ligation. Unless contrary indicated by co-existing medical conditions, closure of the ductus will be sought in any infant with symptomatic PDA and ventilatory failure.

U. RETINOPATHY:

Diagnosis of retinopathy of prematurity greater than Grade I and documented by an ophthalmologist using indirect ophthalmoscopy.

16. PDA WITH CHF:

Check appropriate box and if "yes" check treatment used and the date treatment was initiated. Congestive heart failure is defined as a minimum of cardiomegaly and increased pulmonary vascularity secondary to the shunt.

17. PERIVENTRICULAR LEUKOMALACIA:

(PVL) is an increased density of the white matter of the brain in the periventricular area distince from any areas of hemorrhage. This diagnosis must be made by ultrasound.

18. IVH:

First detected intraventricular hemorrhage. IVH is the term that is defined as hemorrhage of any size, either unilateral or bilateral, occurring in the periventricular white matter of the neonatal brain as diagnosed by either ultrasound, catscan, autopsy, or clinically by the presence of typical clinical constellation of seizures, comatose state, sudden fall in blood pressure, sudden fall in hematocrit, and bulging anterior fontanelle. The grade of intraventricular hemorrhage will be defined as 1, 2, 3, or 4. (Papille grading system).

19. POST HEMORRHAGIC HYDROCEPHALUS:

This term will define as evidence of the development or persistence of ventriculomegaly, with greater than usual head circumference growth.

20. SEIZURES:

If seizures present, record whether one or more episodes occurred, and report the ECG results.

21. CULTURE PROVEN INFECTIONS:

These refer to clinically significant infections that have been confirmed by culture of the appropriate site. This will include all positive blood cultures, endotracheal secretions, urine when sample aseptically collected, positive CSF culture as well as positive cultures from obvious skin infections or abscesses. Do not enter positive cultures that were considered contaminants. Record the date at the site from which first positive culture was obtained.

22. HIGHEST BILIRUBIN:

Enter highest total bilirubin and date it was obtained. Enter highest direct and indirect bilirubins and the dates obtained. These values may occur on different days.

23. MEDICATIONS:

Indicate date medication was first begun and the total number of days for each type of therapy. Count the total number of days when repeated course of treatments are given.

A. ANTIBIOTICS:

Self-explanatory.

B. METHYLXANTHINES:

Either a theophylline containing compound or caffeine.

C. BRONCHODILATORS:

Self-explanatory.

D. MUSCLE RELAXANT:

This refers to paralytic agents such as pancuronium. Do not check this category for use of sedation or use of succinylcholine for intubation.

E. SEDATION:

This refers to drugs such a phenobarbital, chloral hydrate or morphine when used for sedation. When these agents are used for either control of pain or as anticonvulsants this box should not be checked.

F. ANTI-SEIZURE:

Anticonvulsants for treatment of seizures.

G. VOLUME EXPANSION:

Blood or colloid specifically for the expansion of intravascular volume, e.g., for treatment of hyptotension, or oliguric states. Do not check this box for routine transfusions.

H. VASODILATORS:

Self-explanatory.

I. VASOPRESSOR AGENTS:

Self-explanatory.

J. DIURETICS:

Self-explanatory.

K. STEROIDS:

Self-explanatory.

L. BICARBONATES:

Self-explanatory.

24. ENDROTRACHEAL TUBE SUCTIONING:

Record the technique used for suctioning.

25. STUDY OUTCOME:

A. CROSSOVER:

If the infant crossed from the assigned ventilator to the alternate ventilator, check "yes" and enter date of first crossover.

B. ASSIGNED VENTILATION:

Indicate number of days on assigned ventilation.

C. DATE FIRST WEANED TO ENTROTRACHEAL TUBE CPAP:

Indicate date and time baby first weaned OFF IMV to endotracheal CPAP followed by successful extubation not requiring intervention at least for 72 hours.

D. EXTUBATED:

The earliest date and time the patient was extubated and remained extubated for 72 or more hours. How many days on endotracheal tube CPAP?

E. DAYS ON NASAL OR PHARYNGEAL CPAP:

Days on noninvasive CPAP (nasal or pharygeal) following first extubation that did not require reintubation for at least 72 hours.

F. DAYS ON O_2 THERAPY:

Total days in supplemental oxygen during hospital stay. Days in another hospital on oxygen should be included. Days receiving home O_2 should not be included. Home O_2 therapy will be recorded on follow-up forms.

G. ROOM AIR DATE:

The date the patient is weaned from all supplemental oxygen for a period of at least 72 hours.

H. WAS THE BABY ON SUPPLEMENTAL OXYGEN AT DAY 28?

I. ENTERAL FEEDING DATE:

The date the patient was initially weaned from all intravenous nutrition and took only enteral feedings. Days the patient received intravenous medications but not intravenous nutrition should not be included.

J. DATE ON WHICH 90 cal/kg REACHED:

The date the patient first had an enteral intake of 90 cal/kg/day or greater.

K. Radiographic changes at 28 ± 7 days.

26. PATIENT STATUS:

The twenty-eight day status and <u>all</u> events up to the final disposition (discharge to home or death) should be recorded as well as whether the infant was receiving supplementary O_2 therapy or ventilation at the time of the event.

For example, if a baby has expired or has been discharged to <u>home</u> on the 28th day, that would be the final disposition of the baby and the form could be sent to the Coordinating Center. If the baby is

still in the original hospital or has been transferred to another hospital on the 28th day (Part A or C), that section should be filled out in full, but the form is not yet complete.

If Part A or C is the 28th day status, all subsequent events should be reported until the final disposition of the baby is known. If a baby is still in the original hospital on the 28th day, then transferred to another hospital on the 35th day, and discharged to home on the 50th day, all of these events must be reported in full. The form should not be sent to the Coordinating Center until final disposition (discharged to home or death) of the baby can be reported.

A. STILL IN HOSPITAL:

If the baby was in the <u>original</u> hospital on the 28th day, record the date and indicate whether the baby was on a ventilator or O_2 therapy.

B. DISCHARGED TO HOME:

The date the baby was discharged to home whether made from the ICU or from another hospital, and whether the baby was discharged on supplemental oxygen therapy.

C. DISCHARGED TO OTHER HOSPITAL:

Self-explanatory.

D. DIED:

If infant expired, check whether autopsy done.

SIGNATURE OF CLINICAL COORDINATOR

DATE FORM COMPLETED

D. Flow Data Form

This form must be completed on every randomized infant in the study.

1. INFANT ID:

   Affix the infant's ID label.

2. DATE OF BIRTH:

   Record month, day, year using leading zeros. For example, February 5, 1986, should be recorded as 020586.

3. SEX:

   Self-explanatory.

4. VENTILATOR CHANGES:

   Record make and model and serial number of ventilator other than initial assignment as well as starting and ending date and time. Also, record any period the infant is off the ventilator for 72 hours or more, regardless of machine type or serial number. Record any changes between treatment arms (HFV to CMV or vice versa) as well as changes within treatment arms (to different models), changes within a model are recorded (i.e., one Sechrist to another), and a change from a Sechrist to a BP 200 is also recorded.

I. BLOOD GASES, VENTILATOR, CARDIAC VARIABLES AND MEDICATIONS:

Pre I and Pre II are the measurements used as a basis for entry and must be obtained on CMV for infants weighing more than 1250 grams.

Pre-entry -- this reading is taken after the infant has been randomized but before experimental ventilation begun if the lapse in time is greater than one hour since the Pre II for infants

greater than 1250 grams at birth; it is required in all infants with a birthweight of 1250 grams or less.

Hours 2, 4, and 6 should be done within approximately 30 minutes.

Hours 12, 18, 24, 30 and 36 should be done within approximately 2 hours.

Hours 48, 60, 72, 84, and 96 should be done within approximately 4 hours.

On the 5th day after entry and thereafter, blood gases should be taken as close to 7am as possible. Record weekly after 28 days.

1. RESPIRATORY SUPPORT

   A. CMV:

      Self-explanatory.

   B. HMV:

      Self-explanatory.

   C. CPAP (Nasal):

      Self-explanatory.

   D. NASAL CANNULA/PRONGS:

      Self-explanatory.

   E. HOOD:

      Self-explanatory

2. BLOOD GASES

   DATE

   Self-explanatory.

   TIME

   Use 24-hour clock. Midnight = 2400 hours; 1 minute past midnight=0001.

Code the number which indicates the source of blood gas data. All blood gases should be obtained as close to the exact time as possible. In recording data, the descending order of preference for PaO_2, is arterial, transcutaneous, or then capillary. If transcutaneous monitoring is being used, the recording of pH and $PaCO_2$ is at the discretion of the clinician but is recommended at least at the time indicated.

PaO_2 and $PaCO_2$: These should be measured to nearest integer in mm Hg.

pH: This should be rounded off to 2 decimal places.

3. PERCENT O_2:

CPAP nasal cannula or head should only be recorded after an infant has been extubated. Before 2 hours only CMV may be used.

a. O_2 should be expressed as a percent to the nearest integer for both types of ventilation.

b. nasal cannula should be expressed as mL/minutes of 100% oxygen.

4&5. VENTILATOR VARIABLES:

The section for High Frequency Ventilation (4.a) should be filled out if the baby is on HFV at the time the blood gases are drawn and the section for Conventional Ventilation (5) should be filled out if the baby is on CMV. During the acute phase of the treatment when sighs are given (i.e., within 96 hours), if a baby is on HFV and receiving

sighs of at least 1 per hour, the section on sigh data should be filled out. Measurements should be rounded off to the nearest deci mal.

Ventilator Rate: record rate in cpm or cph for CMV and in Hz for HFV

Stroke Volume: record in milliliters for HFV

Amplitude: record in centimeters of water for HFV

PIP:

Inspiratory Time: record in seconds for CMV

PEEP: record in centimeters of water for CMV

Paw: record in centimeters of water to one decimal place

Flow Rate: record in liters for minute to the nearest whole number

IHFO

6. CARDIAC/RESPIRATORY VARIABLES:

Respiratory and heart rates are to be recorded at the times indicated and may be abstracted from nursing notes if taken during periods of agitation. Measurements should be taken up to and including 48 hours.

Heart rate: record the beats per minute.

Spontaneous Respiratory rate: record rate of breaths per minute.

Blood pressure: For invasive methods record the systolic and diastolic blood pressure. Mean values should not be recorded for Doppler measurements. Record the method by which blood pressure was obtained.

Direct Blood Pressure: not required but may be recorded from an arterial catheter.

Indirect Blood Pressure may be recorded from Doppler or oscillometric data.

7. MEDICATIONS:

Record which medications have been used, the type, and the dosage.

II. NUTRITION:

Day 0 begins at time of birth and extends until the beginning of the next full nursing administrative 24-hour period which is defined as day 1. Continue to record weekly after Day 28 until discharged or transferred.

Total parenteral fluid intake: this includes crystalloid, colloid, blood, blood products, bicarbonate, all flushes, and other fluid administered by parenteral route.

Total enteral fluid intake: this includes total enteral intake of water, breast milk or formula but not medications.

Total caloric intake: this includes parenteral amino acids, carbohydrates and fats as well as enteral nutrition.

Weight: this should be recorded to the nearest 10 grams.

Bed: Self-explanatory.

Urine output: record in ml/24 hours.

SIGNATURE OF CLINICAL COORDINATOR

DATE

E. Cross-Over Form

The Crossover Form should be completed every time a randomized infant meets crossover criteria whether or not the infant was actually switched to the other mode of ventilation. It should be filled out in addition to the Flow Data Form. It should also be completed if an infant was switched without meeting criteria. For infants not switched, Questions 1-5 and Question 7-8 should be answered.

It is possible to have more than one crossover in type of ventilator therapy during treatment. For either group (infants assigned to CMV or HFV), failure of treatment (a mandatory switch of ventilators) will occur when an infant has either one of the following:

1. Both a $PaCO_2 > 65$ torr and a $PaO_2 < 45$ torr in an F_IO_2 of 1.0 and a Paw of at least 15 cm H_2O, or
2. A PaO_2 of < 35 torr alone with a Paw of at least 15 cm H_2O in F_IO_2 of 1.0,
3. A $PaCO_2 > 75$ unless this gas level was artificially raised by the physician.

The poor arterial blood gas values ($PaCO_2$, PaO_2) must persist in spite of two ventilator setting changes with accompanying blood gases within one hour. An attempt will be made to obtain two successive blood gases or ventilator setting changes within one hour after encountering an unacceptable blood gas. An acute event with temporary deterioration in condition, such as pneumothorax, is not criteria for switchover.

If a baby reaches criteria and is switched to the other ventilator, three things may appear on the new form of treatment.

1. Condition get worse:

   It is assumed that the infant was switched to this new ventilator because either the PaO_2 was < 45 mm Hg and $PaCO_2$ > 65 mm Hg or PaO_2 was < than 35 with increased Paw. Therefore:

   A. If the arterial blood gas values worsen greater than 10 mm Hg for either PaO_2 or $PaCO_2$, the infant will be switched back to the original ventilator.

   B. Observation of the infant for as short a period as 15 minutes with at least one arterial blood gas will be performed before deciding that the baby is worse and needs to have the ventilator type changed.

2. Condition remains the same: stays up to six hours but then must go back to previous therapy.

3. Condition improves: must leave infant on the present form of ventilator.

For an explanation of the variables to be recorded, see the instructions for the Flow Data Form.

F. Protocol Interruption Form

This form must be completed whenever the assigned ventilatory therapy is stopped for more than one hour.

G. Termination Form

A termination form should be completed and sent to the Coordinating Center when an infant terminates from the study for any reason. Termination means withdrawal from the data collection part of the study. Withdrawal from treatment does not constitute termination.

Causes of death should be those determined at autopsy if such results are available. If no such information is available, the causes may be taken from the death certificate.

H. Autopsy Form

To be completed when an autopsy has been performed.

I. Interim Visit Form

This examination is to be performed nine months from the term date. The gestational age at birth will be assigned during the neonatal period by the established protocol. This age must remain consistent throughout the follow-up study.

1. INFANT ID:

   Self-explanatory.

2. DATE OF EXAMINATION:

   Self-explanatory.

3. POST-TERM AGE:

   The post term age is the age in months from the due date (expected date of delivery).

4. STATUS AT TIME OF EXAMINATION:

   Self-explanatory.

5. VENTILATORY SUPPORT:

   The ventilatory aid refers to the device in use on the day of examination. The amount of supplemental oxygen therapy should be noted when known. If low flow oxygen is used, mark unknown. If oxygen was discontinued after discharge, mark date. Use decimal point for recording flow rate (i.e., 1/8 = 0.125).

6. CURRENT MEDICATIONS:

A. DIURETICS:

There is no need to specify the specific type of diuretic.

B. BRONCHODILATORS:

Indicate the specific type of bronchodilator, i.e., systemic such as theophylline or aerosals such as a bronkosol.

C. OTHER:

If other medication is involved, note only the general type, e.g., antibiotic, phenobarbital. If theophylline is used primarily for apnea, note in section C.

7. RESPIRATORY TRACT COMPLICATIONS:

We are interested in the number of respiratory complications. Most of these complications will be in the form of superimposed upper and lower respiratory tract infections.

A. INFECTIONS:

Note the number of infections. "Otitis" includes middle ear disease treated by antibiotics. "Upper respiratory infections" include croup, cold, etc. "Lower respiratory infections" include pneumonia, bronchiolitis, bronchitis, etc. which has required medical intervention.

B. HOSPITAL ADMISSIONS:

Note the total number of hospital admissions resulting from these infections and the total number of days in hospital. Record "0" if none.

C. OTHER HOSPITAL ADMISSIONS:

Note the number of hospital admissions for respiratory complications other than superimposed infection noting the type of complication and the total number of days in hospital.

8. HOSPITAL VISITS:

This section is related to all hospital admissions (e.g., hernia repair and all respiratory hospitalizations).

9. CONDITION DURING EXAM:

The condition during the exam relates to the general state of the infant. It is to determine whether the examination is a reliable indication of the baby's status. If the baby is ill, excessively irritable or overtired, please specify unsatisfactory and the reason.

10. GROWTH MEASUREMENTS:

A. WEIGHT:

Weight is to be done on a balanced scale.

B. LENGTH:

Crown-heel, supine measurement is to be performed with an appropriate measuring board. The full stretch length is to be utilized.

C. HEAD CIRCUMFERENCE:

The largest occipital-frontal head circumference is to be determined using narrow paper or metal tape.

D. TEMPERATURE:

Record Axillary celsius temperature.

11. RESPIRATORY SYSTEM: To be examined in the resting state. Examination should be repeated after exercise. Exercise may be achieved by pulling to the sitting position (x3) or by any form of active physical movement.

To be examined in the resting state.

A. RATE:

Self-explanatory.

B. RETRACTIONS:

Intercostal, subcostal or suprasternal retraction should be included.

C. STRIDOR:

Stridor is a harsh audible sound due to upper airway obstruction, e.g., croup.

D. WHEEZING:

Wheezing is due to lower respiratory involvement and is similar to the audible sound in infants with bronchiolitis or asthma.

E. PROLONGED EXPIRATORY PHASE:

Prolonged expiratory phase will be a subjective measure. It can include end expiratory grunting and/or wheezing as heard by the stethoscope.

F. RALES, RHONCHI, ETC.:

Includes all adventitious sounds heard with the stethoscope and related to lower respiratory tract pathology.

G. CYANOSIS:

This includes generalized or perioral cyanosis.

H. CLUBBING:

Self-explanatory.

12. AIRWAY PATHOLOGY:

A. VOICE QUALITY:

This should be determined during crying.

1. Corresponds to a mute child.
2. Corresponds to a sound that is of low frequency.
3. Corresponds to a sound that is of low intensity.
4. Self-explanatory.
5. This section to be marked for infants with endotracheal tube, tracheostomy tube in place or for infants who did not vocalize.

B. NOSE/MOUTH:

1. Self-explanatory.

2. Iatrogenic scarring or asymmetry.

3. Acquired deformation of the palate.

C. TRACHEOSTOMY:

Present at time of examination.

D. SUBGLOTTIC STENOSIS:

This diagnosis will depend upon previous investigation either radiologic or direct vision. Suspect stenosis should not be included.

13. CARDIOVASCULAR SYSTEM:

These determinations should be done during the resting state.

A. HEART RATE:

Self-explanatory.

B. BLOOD PRESSURE:

Self-explanatory.

C. ABNORMAL RHYTHM:

Self-explanatory.

D. MURMUR:

If possible, give specific diagnosis (e.g., PDA, VSD, flow murmur).

E. EXCESS PRECORDIAL ACTIVITY:

Refers to clinical signs of cardiomegaly.

F. OTHER ABNORMAL FINDINGS:

Self-explanatory.

14. ABDOMEN:

A. LIVER:

Should be measured in the mid-clavicular line.

B. SPLEEN:

Self-explanatory.

C. INGUINAL HERNIA:

If yes, indicate whether the condition has been surgically corrected.

D. OTHER ABNORMALITIES:

Self-explanatory.

15. EYES:

A. PUPILS:

Self-explanatory.

B. LIGHT REFLEX:

Self-explanatory.

C. FIXES:

Any object may be used, either the examiner's face or a specific object. Attempt to get fixation and following at both near sites and distant. The infant should follow the object past the mid-line.

D. FOLLOWS:

See 15.C

E. NYSTAGMUS:

Self-explanatory.

F. OTHER ABNORMALITIES

16. HEARING:

A. RESPONDS TO BELL:

A bell should be rung approximately two feet from the ear. A response includes stilling, alerting, blinking. Response should be repeatable.

B. RESPONDS TO VOICE:

The examiner should speak to the baby while he/she is out of line of the baby's visiion. Response is as in A.

17. NEUROLOGICAL ASSESSMENT:

The purpose of the neurological assessment is to determine the presence or absence of suspicious signs of major neurologic defects.

A. TONE:

1. NECK EXTENSORS:

The neck extensors usually include the extensors of the shoulders. A baby with increased tone in these muscle groups tends to arch his head back in the prone position and has an exaggerated head lag on traction response. Decreased tone in the neck extensors is reflected by a very unsteady head control.

2. HAMSTRINGS:

Evaluate tone in the lower limb in the supine position by determining resistance to passive flexion of the hip, abduction of the hip and dorsiflexion of the ankle. Increased tone in the suspect muscle groups can be verified by palpation of the hamstrings, hip abductor and gastrocnemei when the muscles are in a stretched position.

3. HIP ADDUCTORS:

See A.2

4. GASTROCNEMEI:

See A.2

5. TRUNK:

Assess the tone of trunk muscles in the sitting and upright position.

B. REFLEXES:

1. DEEP TENDON REFLEXES:

Test tendon reflexes with a patellar hammer or by digital percussion. Note whether the reflex is accompanied with clonus.

2. PRIMARY REFLEXES:

Note whether the primary reflexes are still present. The moro, tonic and primary standing reflex should be absent at this age. Cortical inhibition of the primary palmar grasp should be well developed so that this reflex is no longer obligatory.

C. MOVEMENTS:

1. VOLUNTARY MOVEMENTS:

Observe the baby lying at rest in the supine position and note the quality of spontaneous voluntary movements (i.e., kicking, hands to the mouth, etc.). Note whether the movement occurs to the same degree on both sides.

Hydrocephalus is defined as progressive intraventricular dilation as determined by ultrasound or CAT scan accompanied by clinical signs of increased intracranial pressure (accelerated growth in head circumference). If this process is self-resolving after more than 3 weeks, it should be termed "arrested hydrocephalus." If the condition continues to progress requiring shunting, the date of the first shunt insertion should be noted.

(from Fitzhardinge 6/14/88)

2. INVOLUNTARY MOVEMENTS:

Involuntary movements includes jerking or twitching actions that do not appear to be under the infant's control. Information on involuntary movements may be obtained by history.

Seizures may be of any type: tonic-clonic, focal, salaam type. Jitteriness refers to a tremulous movement of the extremities which can be stopped by holding the extremity.

D. HYDROCEPHALUS:

Hydrocephalus is defined as progressive ventricular dilatation as determined by ultrasound or CT scan accompanied by clinical signs of increased intracranial pressure.

18. CHEST X-RAY:

This section is limited to those babies who were diagnosed in the newborn period as having chronic lung disease. It is important to document whether or not the baby has a normal chest x-ray subsequent to the diagnosis of chronic lung disease. If a previous x-ray has been performed and is available for assessment by the study radiologist, a repeat x-ray at this examination is unnecessary. The evaluation of the x-rays should be performed by a consistent team of radiologists who are unaware of the prior history and treatment of the infant.

19. TOTAL CHLORAL HYDRATE:

Measure in mg.

20. O_2 SATURATION:

Background: Assessment of overall gas exchange in 9 month olds is at best difficult. Measurement of skin surface oxygen and carbon dioxide tensions using standard electrodes have limitations in this age group,

although they give valuable information about changes in clinical status. These limitations appear to be exaggerated in infants with bronchopulmonary dysplasia, possibly due to derangements of the skin microvasculature. Pulse oximetry has been recently validated for use both in the newborn period and in older children during intensive care. Therefore, this technique should be used to assess the oxygen saturation of these children, particularly with respect to derangements of ventilation/perfusion which may be related to their early ventilatory management.

Preliminary computations regarding the estimated arterial saturation in infants with a 2 compartment model of ventilation and perfusion have been made. Areas with low ventilation to perfusion ratio, have a lowered alveolar PO_2, due to the consumption of oxygen from the alveolus by the mixed venous blood. The lower the alveolar PO_2 is exaggerated by lowering the inspired oxygen tension, as evidenced by the intolerance of altitude of patients with chronic lung disease. Altitude will be simulated by giving these infants 17% oxygen to breathe (equivalent room air at an elevation of 6,000 feet) to bring out abnormalities of oxygenation due to mismatch of ventilation and perfusion. In a two compartment model, if only 10% of the alveolar ventilation is distributed to areas where the ventilation/perfusion ratio of 0.2, the overall ventilation/perfusion ratio would be 0.92. An infant under these circumstances would have an estimated arterial saturation of 88% on room air which would drop to 80% - 82% while breathing 17% oxygen. Sixteen infants aged 6-8 months with a pulse oximeter (Nelcor model N-100) have been studied and have shown a coefficient of variation of the measurement within any patient of 0.8%

and 1.2% saturation while they breathed room air or 17% oxygen, respectively. The average change in absolute saturation between these conditions was 5.4 ± 2.9% saturation for these infants. It is expected that even small derangements in the ventilation/perfusion ratio representing a small fraction of the alveolar ventilation should produce a detectable change in oxygen saturation between breathing room air or 17% oxygen.

The assessment of overall gas exchange in each infant will be applied while sleeping, prior to the forced expired volume maneuver. 17% oxygen should be administered to the infant by means of head hood. The 17% oxygen mixture should also be mixed and analyzed to 0.1%, and this gas mixture is available at a reasonable cost. A pulse oximeter (Nelcor model N-100) will be attached to a foot or hand. Saturation will be recorded for a one minute baseline period on the worksheet. Then 17% oxygen should be administered for 6 minutes while recording the oxygen saturation on the worksheet. During the first five minutes, the saturation will be recorded on the worksheet every minute. During the sixth minute, the saturation will be recorded every 10 seconds by the technician, using the digital readout. The mean and standard deviation for the baseline period while breathing room air, and for the fifth minute of breathing 17% oxygen will be computed and recorded. The procedure will be terminated if the saturation drops below 80%. If the oxygen saturation values are unstable or the infant arouses, the test will be repeated.

21. RESISTANCE AND COMPLIANCE

Measurements of pulmonary mechanics are performed without sedation in neonates and using 50 mg/kg of chloral hydrate given orally in older

infants. Tidal flow is measured with FLEISCH pneumotachograph (Oem Medical, Richmond, Virginia) size 00 in neonates and size 0 in older infants. The pneumotachograph is attached to a face mask. Different size masks should be available for ideal fit. The risks of using a mask are nasal obstruction, pharyngeal obstruction by pushing the mandible backwards, hyperventilation and leaks. Petroleum jelly or putty may be used to prevent leaks. The differential pressure output from the pneumotachograph is measured with a Validyne transducer (MP45, Validyne, Northridge, CA) and amplified by a Gould pressure amplifier (Gould, Cleveland, Ohio). Other brands of amplifiers may be used. The pneumotachograph is calibrated using constant flows and a Tissot spirometer, or a calibrated mechanical or electronic flow meter (Matheson, East Rutherford, NJ) before each test. The pneumotachograph needs to be checked for linearity once a month. Tidal volume is obtained by electrical integration of the flow signal using a Gould or similar integrator amplifier. Calibration of tidal volume is done before and after each study using a calibrated glass syringe. An 8 French water filled feeding tube is placed in the lower esophagus in order to measure esophageal pressure by means of a Statham ID P23 or similar transducer and a Gould pressure amplifier calibrated with a water manometer. The tip of the tube is positioned in the lower portion of the esophagus by recording pressures while pulling the tube from the stomach into the esophagus. This position reduces cardiac artifact and provides the most reliable signal. The accuracy of the esophageal pressure signal is tested by comparing airway and esophageal pressure

during airway occlusion.[1] The esophageal tube needs to be flushed immediately before each recording to eliminate air bubbles. Air flow, tidal volume, esophageal pressure and airway pressure are recorded simultaneously on a recorder (Gould 260) at a speed of 25 or 50 mm/sec. Other amplifying and recording equipment may be used.

Ventilatory measurements are done during quiet, regular and unobstructed breathing. Inspiratory and expiratory time together with tidal volume are determined as an average from the rapid recording of flow and volume (25 mm/sec) of at least 10 breaths.

Minute ventilation is obtained by adding the tidal volumes of at least 30 sec of recording during quiet regular breathing.

Inspiratory pressure is determined as an average from the esophageal pressure recording of at least 10 breaths. The pressure change from zero to maximal negative deflection is measured during each inspiration.

Lung compliance is calculated by dividing tidal volume by the esophageal pressure change measured at the moment of zero flow between inspiration and expiration. Total pulmonary resistance is calculated at mid-tidal volume by determining the pressure difference between the points of mid-inspiration and mid-expiration and dividing this by the sum of the inspiratory and expiratory flows measured at the same points

1 Beardsmore CS, Helms S, Stocks J, Hatch DJ, Silverman M. Improved esophageal techniques for use in infants. J. Appl. Physio. 1980; 49:735-742.

in time.[2] [3] Krieger's paper shows how and where to make the different pressure measurements during a respiratory cycle.

Several of the older infants who will receive chloral hydrate may develop snoring during sleep. This will result in an increase of their inspiratory and total pulmonary resistance. When this occurs, an effort should be made to relieve the obstruction by positioning the infant or by extending the neck and pushing the mandible forward until snoring disappears and a minimal esophageal pressure change is obtained. Snoring has a minimal effect on expiratory resistance and therefore this value should be calculated in all infants over 3 months of age. Expiratory resistance can be calculated following the method described by Krieger. In newborn infants, snoring is unusual and total pulmonary resistance should be determined because the frequent non-linearity of their pressure volume curve does not allow the accurate separation of expiratory and inspiratory resistance.[4] Improper position of the face mask may lead to airway obstruction. This can be

2 Cook CD, Sutherland JM, Segal S, Cherry RB, Mead J, McIlroy MB, Smith CA. Studies of respiratory physiology in the newborn infant. III. Measurements of mechanics of respiration. J. Clin. Invest. 1957; 36:440-448.

3 Krieger I. Studies on mechanics of respiration in infancy. Am. J. Dis. Child. 1963; 105:51-60.

4 Tapia IL, Gerhardt T, Goldman S, Hehre D, Feller R, Bancalari E. Influence of tidal volume on lung compliance and resistance in infants with acute respiratory failure. Clin. Res. 1982; 30:908A.

detected by the sudden increase in esophageal pressure after the mask have been attached. This change in esophageal pressure should be minimal initially, but may increase because of rebreathing. At least 10 breaths need to be analyzed for compliance and resistance in each infant and the values averaged. The individual results of compliance and conductance (the reciprocal of resistance) need to be related to body weight and length in order to compare the two different groups of infants.

22. FORCED EXPIRATORY MANEUVERS:

All infants undergoing testing are given chloral hydrate in a dose of 50 mg/kg upon entry into the infant testing laboratory. If the infant is not sleeping soundly within 30-45 minutes, a second dose of chloral hydrate ranging from 25-50 mg/kg is given. The total dose of chloral hydrate never exceeds 100 mg/kg. When the infant is felt to be sleeping soundly, it is wrapped in an inflatable jacket which fully surrounds the chest and abdomen (the Hammersmith Jacket). Flow is measured at the mouth using a Bennett face mask connected to a Hans-Rudolph pneumotachometer designed to be linear to 1 liter/second. Pressure drop across the pneumotach is measured using a Validyne ± 2 cm of water pressure transducer and Hewlett Packard carrier amplifier. Volume is obtained as the integral of flow from the Hewlett Packard amplifier. Both flow and volume signals are displayed on a Tektronics Storage Oscilloscope.

The Hammersmith Jacket is connected by wide-bore tubing to a 40-gallon plastic barrel which serves as a positive pressure reservoir. jacket pressure is measured using a Validyne ± 50 cm of H_2O pressure transducer and Hewlett Packard Carrier Amplifier. Reservoir pressure

is displayed constantly on a 0-200 cm of H_2O pressure gauge. An automatic 3-way direction valve (Hans-Rudolph model 8500C) is used to both direct pressure into the jacket and release pressure from it after the maneuver. Opening the pressure reservoir to the jacket results in a rise of jacket pressure to peak levels in less than 100 milliseconds. Reversal of the valve opens the jacket immediately to atmospheric pressure.

Partial maximal flow volume curves are collected in the following manner. The infant's tidal flow volume loops are observed on the oscilloscope screen. When FRC appears to be stable, three tidal efforts documenting the position of FRC are recorded. At end inspiration following the third tidal breath, the automatic valve on the pressure reservoir is triggered and the jacket is inflated for 0.5 - 1.0 seconds. This produces expiratory flows that exceed flows recorded during tidal breathing and squeezes the infant to lung volumes lower than FRC. Jacket pressures used for initial compressions are approximately 40 cm of water. Following an initial compressure, pressure in the reservoir is increased so as to produce peak jacket pressures during chest compression of approximately 60 cm of water and the foregoing procedure is repeated. Pressure is increased in similar intervals until the forced expiratory flow measured at the point of FRC is the same at two consecutive pressures. Jacket pressures which produce a "maximal" flow have been found to fall between 40 and 100 cm of water and on average occur at 60-70 cm of water. Three reproducible partial forced expiratory efforts are collected and the average of these three measurements is reported as the flow at FRC. The pressure in the jacket during each maneuver is also recorded on the oscilloscope

screen. Six to ten "squeezes" are usually required to obtain the above data.

23. FUNCTIONAL RESIDUAL CAPACITY:

Functional Residual Capacity is determined by N_2 washout. The open circuit method has been described in detail previously (Gerhardt T, Here D, Bancalari E. A simple method of measuring functional residual capacity by N_2 washout in small animals and newborn infants. Pediatrics Research 19:1165-1169, 1985).

The design of the sytem used to measure FRC is shown in the figure. It consists of a gas mixer with a flow meter, connected to oxygen and helium supplies, which delivers a continuous and stable flow of 100% O_2 or any oxygen/helium mixture. The gas is warmed and humidified and delivered to the infant through a T-tube by mask. A three-way valve may be placed between mask and T-tube. From the exhalation part of the T-tube the gas passes through a mixing chamber (500 ml glass bottle). The N_2 concentration of the gas leaving the mixing chamber is analyzed continuously by a rapid N_2 analyzer or mass spectrometer. After the sampling site, the gas flows through additional tubing to prevent drawing room air into the sampling site during an unexpected sigh of the infant. The nitrogen concentration signal is integrated and displayed on a recorder.

Calibration can be done by attaching a 50 ml syringe filled with room air to the T-tube. Moving the piston back and forth in small strokes will slowly wash out the gas from the syringe and add its N_2 content to the nitrogen free gas passing through the T-tube. The signal obtained from the integrator is proportional to the amount of 39 ml N_2 (78% N_2 in room air).

The accuracy of the method depends on three conditions:

1. The background flow delivered by the flow meter is constant.
2. The exhaled N_2 is well mixed with the gas flowing through the system before analyzing the N_2 concentration.
3. Absence of leaks around the mask.

The background flow through the system is adjusted to the infant's peak inspiratory flow. This prevents rebreathing, and the N_2 concentration in the mixing chamber rises to 5-10% in all patients independent of their size.

The mixing chamber dampens breath to breath changes in N_2 concentration resulting in a typical washout curve with a fast rise and a gradual decrease in N_2 concentration over the entire duration of the washout. The larger the chamber and the lower the flow the more pronounced is this dampening effect. A container with a volume ten times the tidal volume of the subject tested, provides good mixing as demonstrated by the reproducibility of the N_2 measurements. Poor mixing results in an overestimation and a larger variability of the determinations.

Leaks around the mask can be detected from baseline changes if a pneumotachograph is placed into the circuit. The amount of N_2 washed out can be calculated by the following measurements:

1. Washout of "v" ml of air from a syringe into the circuit results in the integrated N_2 concentration of "c" chart divisions.
2. The N_2 washout in the patient yields "n" chart division.

$$\text{Total } N_2 \text{ washed out: } V_{N_2} = \frac{0.78v \cdot n}{c}$$

FRC is calculated according to the equation:

$$FRC = \frac{V_{N_2}}{F_AN_{2,a} - F_AN_{2,p}}$$

V_{N_2} = Total volume of washed out N_2

$F_AN_{2,a}$ = Fraction of alveolar N_2 before washout

$F_AN_{2,p}$ = Fraction of alveolar N_2 at end of washout

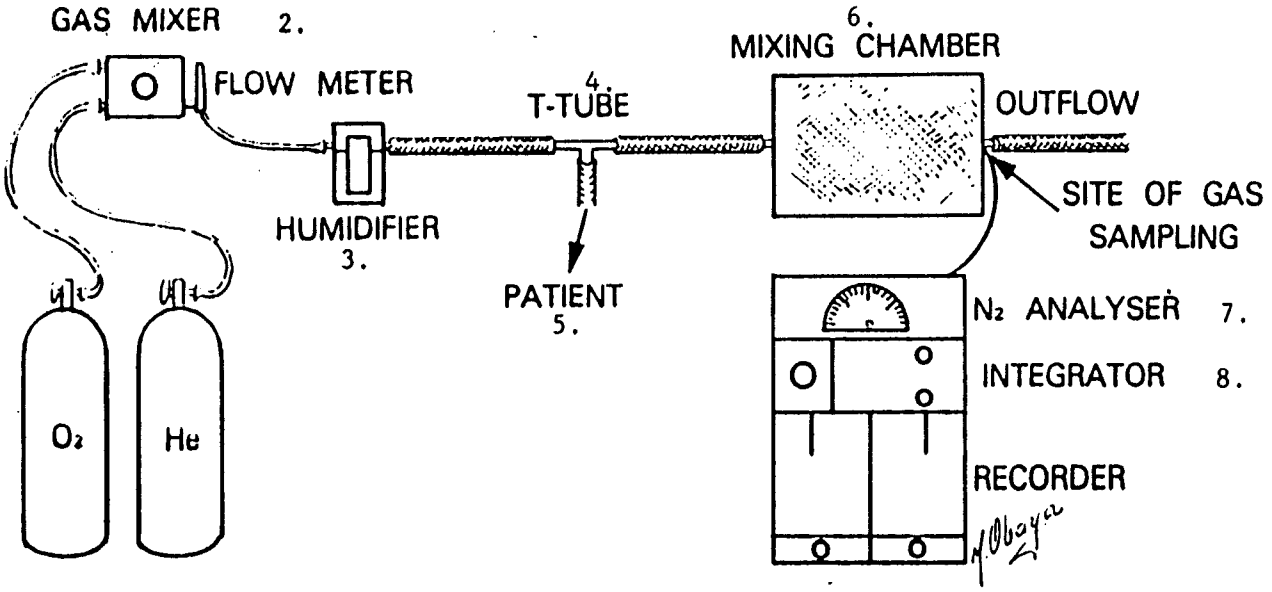
Measurements in infants breathing RA have shown an $F_AN_{2,a}$ of 0.79 - 0.80 $F_AN_{2,p}$. After two minutes of breathing the nitrogen free gas was 0.01 - 0.02. It is therefore reasonable to assume a value of 0.78 for the difference $F_AN_{2,a} - F_AN_{2,p}$.

The equation can then be simplified:

$$FRC = \frac{V.n}{c}$$

The calibration procedure should be repeated three times and the integrated N_2 concentration should not differ more than 1-2%.

FRC measurements are also repeated three times and averaged. Results should be within 10% of each other and need to be corrected from the temperature and water vapor saturation of the test gas to BTPS conditions.



1. Gas Source Wall O_2 is fine
2. Flow meter To keep flow through system constant. Set above inspiratory flow of infant.
3. Humidifier, Warmer Any leak free system used in the nursery is fine
4. T-piece and corrugated respiratory tubing for connection
5. Connection to patient by nose piece or mask
6. Mixing chamber - Approximately 1000 ml. Soda lime cartridge or IV bottle
7. N_2 Analyser - For example Med Science 505 D
8. Integrator To integrate N_2 signal. Balanced to give straight line with 100% O_2 in system

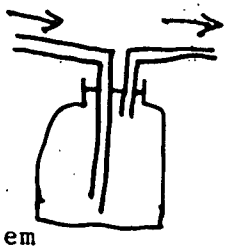


FIGURE 1 Functional Residual Capacity

J. Final Visit Form

The primary purpose of the final exam is to evaluate neurological development. This examination should be performed as close to the age of 18 months from the term date as possible. The child should not be younger than 17 months or older than 19 months from term.

1. INFANT ID:

   Self-explanatory.

2. DATE OF EXAMINATION:

   Self-explanatory.

3. POST-TERM AGE:

   The post-term age is the age in months from the due date (expected date of delivery).

4. STATUS AT TIME OF EXAMINATION:

   Self-explanatory.

5. VENTILATION:

   The ventilatory aid refers to the device in use on the day of examination. If the ventilation was discontinued the day before, column 5 should be noted. The amount of supplemental oxygen therapy should be noted when known. If low flow oxygen is used, mark unknown. If oxygen was discontinued after discharge, mark date.

6. CURRENT MEDICATIONS:

   A. DIURETICS:

      There is no need to specify the specific type of diuretic.

   B. BRONCHODILATORS:

      There is no need to specify the specific type of bronchodilator.

C. OTHER:

If other medication is involved, note only the general type, e.g., antibiotic, phenobarbital. If theophylline is used primarily for apnea, note in Section C.

7. RESPIRATORY TRACT COMPLICATIONS:

We are interested in the number of respiratory complications between the interim and final visit. Most of these complications will be in the form of superimposed upper and lower respiratory tract infections.

A. INFECTIONS:

Note the total number of infections between the two visits. "Otitis" includes middle ear disease treated by antibiotics. "Lower respiratory infection" includes pneumonia, broncholitis, bronchitis, etc. which has required medical intervention.

B. HOSPITAL ADMISSIONS:

Note the total number of hospital admissions resulting from these infections and the total number of days in hospital. If a baby has never been discharged from hospital, this area would be left blank.

C. OTHER HOSPITAL ADMISSIONS:

Note the number of hospital admissions for respiratory complications other than superimposed infection noting the type of complication and the total number of day in hospital.

8. HOSPITAL VISITS:

This section is related to all hospital admissions since the interim visit (e.g., hernia repair and all respiratory hospitalizations).

9. SEIZURES:

Seizures may be diagnosed by history. Distinguish between febrile and nonfebrile.

10. CONDITION DURING EXAM:

The condition during the exam relates to the general state of the infant. It is to determine whether the examination is a reliable indication of the baby's status. If the baby is ill, excessively irritable or overtired, please specify unsatisfactory and the reason.

11. MEASUREMENTS:

A. WEIGHT:

Weight is to be done on a balanced scale.

B. LENGTH:

Crown-heel, supine measurement is to be performed with an appropriate measuring board. The full stretch length is to be utilized.

C. HEAD CIRCUMFERENCE:

The largest occipital-frontal head circumference is to be determined using narrow paper or metal tape.

D. TEMPERATURE:

Record axillary celcius temperature.

12. RESPIRATORY SYSTEM: To be examined in the resting state. Examination should be repeated after exercise. Exercise may be achieved by pulling to the sitting position (x3) or by any form of active physical movement.

To be examined in the resting state.

A. RATE:

Self-explanatory.

B. RETRACTIONS:

Intercostal, subcostal or suprasternal retraction should be included.

C. STRIDOR:

Stridor is a harsh audible sound due to upper airway obstruction, e.g., croup.

D. WHEEZING:

Wheezing is due to lower respiratory involvement and is similar to the audible sound in infants with broncholitis or asthma.

E. PROLONGED EXPIRATION PHASE:

Prolonged expiratory phase will be a subjective measure. It can include end expiratory grunting and/or wheezing as heard by the stethoscope.

F. RALES, RHONCHI, ETC.:

Includes all adventitious sounds heard with the stethoscope and related to lower respiratory tract pathology.

G. CYANOSIS:

This includes generalized or perioral cyanosis.

H. CLUBBING:

Self-explanatory.

13. AIRWAY PATHOLOGY:

A. VOICE QUALITY:

This should be determined during crying.

1. Corresponds to a mute child.
2. Corresponds to a sound that is of low frequency.
3. Corresponds to a sound that is of low intensity.
4. Self-explanatory.
5. This section to be marked for infants with endotracheal tube, tracheostomy tube in place or for infants who did not vocalize.

B. NOSE/MOUTH:

1. Self-explanatory.

2. Iatrogenic scarring or asymmetry.

3. Acquired deformation of the palate.

C. TRACHEOSTOMY:

Present at time of examination.

D. DOCUMENTED SUBGLOTTIC STENOSIS:

This diagnosis will depend upon previous investigation either radiologic or direct vision. Suspect stenosis should not be included.

E. OTHER:

Self-explanatory.

14. CARDIOVASCULAR SYSTEM:

These determinations should be done during the resting state.

A. HEART RATE:

Heart rate should be taken at rest.

B. BLOOD PRESSURE:

Self-explanatory.

C. ABNORMAL RHYTHM:

Self-explanatory.

D. MURMUR:

If possible, give specific diagnosis (e.g., PDA, VSD, flow murmur).

E. EXCESS PRECORDIAL ACTIVITY:

Refers to clinical signs of cardiomegaly.

F. OTHER ABNORMAL FINDINGS:

Self-explanatory.

15.

A. LIVER:

Should be measured in the mid-clavicular line.

B. SPLEEN:

Self-explanatory.

C. INGUINAL HERNIA:

Self-explanatory.

D. OTHER ABNORMALITIES:

Self-explanatory.

16. EYES:

A. PUPILS:

Self-explanatory.

B. LIGHT REFLEXION:

Self-explanatory.

C. FIXES:

Any object may be used, either the examiner's face or a specific object. Attempt to get fixation and following at both near sites and distant. The infant should follow the object past the mid-line.

D. FOLLOWS:

As above.

E. NYSTAGMUS:

Self-explanatory.

F. OTHER:

Self-explanatory.

17. NEUROLOGICAL EXAMINATION:

This examination is the key part of the visit. From this examination we should be able to determine whether the child has a major neurologic deficit, is totally normal, or demonstrates mild or suspicious abnormalities.

A. MOVEMENTS:

Movements refer to voluntary and involuntary movements performed on the part of the baby. Each extremity should be evaluated independently. We are looking for evidence of decreased use of one of the extremities or abnormal posturing or movement of an extremity.

B. TONE:

Tone should be recorded as either increased, decreased or normal for age. Tone should be evaluated in a similar manner as in the previous visits.

C. REFLEXES:

1. Deep tendon reflexes should be elicited in the same manner as at previous visit.
2. Elicit the asymmetric tonic neck reflex in a similar manner to that noted in the first visit. Determine whether, if present, the reflex is obtained in both directions (bilateral) or only in one direction (unilateral).
3. The grasp reflex should be elicited by placing the examiner's digit in the infant's palm on the ulnar side exerting enough pressure to slightly dorsiflex the wrist. A positive grasp reflex consists of a grasp response that cannot be inhibited and is abnormal at this age.

4. Elicit the primary standing reflex in the same manner as with a newborn by supporting the infant at the axilla and allowing weight bearing on the sole of the feet. A positive response is an immediate straightening of the body, standing with a narrow base. This standing pattern can be discriminated from normal voluntary standing by a lack of any balancing maneuver in the primary reflex position. Presence of this reflex is abnormal.

5. The parachute response may be elicited by sudden lowering of the baby in the ventral suspension position with a positive response consisting of abduction of the arms.

6. A positive Babinski consists of dorsiflexion of the great toe following stroking of the sole of the foot.

D. POSTURE ABNORMALITIES:

1. Observe the position of the limbs at rest with particular reference to abnormal positioning of the hands, palmar fisting, and positioning approaching opisthotonus.

2. Evaluate head control in the upright position and determine whether normal or abnormal.

3. Evaluate the sitting position and determine whether abnormal. The child at this age should sit well with a straight back and legs in front of him/her. The child should be able to pivot and reach behind himself and move easily into a standing position.

4. Evaluate the prone position on a firm surface. The infant should be able to quickly get into a crawling position on its hands and knees and move from prone to a sitting position without difficulty.

5. Evaluate the standing position by placing the child on a firm surface in his bare feet. This child should be able to stand with a fairly narrow base without support. (It should not be supported by the observer.) Note whether the weight is born on the soles or on the tip toes. Balance should be easily maintained without the need of arm elevation.

E. GROSS MOTOR:

This section evaluates the gross motor activity. Note whether the function is performed in a normal or abnormal manner. For example, a commando crawl would be recorded as "crawling-present-abnormal".

1. Most infants will refuse to crawl at this age.
2. Most infants will not cruise but will walk unaided.
3. The infant should stand easily by himself using no obvious balancing maneuver.
4. The gait should be heel-toe, narrow based with no higher than hip-level hand guard. The infant should be able to turn easily. If abnormal, please describe (e.g., foot drop on L, tends to drag L foot).
5. The infant should be able to run for approximately 10 feet. Hands may be held high for balance.
6. Note whether the infant can stoop or squat to retrieve an object and then resume normal standing position without use of his hands.

F. FINE MOTOR:

This section evaluates the fine motor development.

1. The pincer grasp should be assessed by asking the child to lift a small object (coin) from a smooth, firm surface. Note also whether the toys are explored using the fingers or whether the toy is taken directly to the mouth for further examination.
2. Note repeated preference for one hand over the other.
3. Note ataxia when reaching for an object.

G. CRANIAL NERVES - MOTOR FUNCTION:

Only the motor function of the cranial nerves will be tested. Abnormalities to be looked for are:

1. Involuntary drooping of the eyelid.
2. Crossing of the eyes.
3. Check range of eye movements and record incomplete movement or lagging of eye movement on one side.
4. Nystagmus.
5. Weakness of the facial muscles.

H. HYDROCEPHALUS:

Hydrocephalus is defined in the same manner as noted in the interim visit. If shunt insertion has been performed, please note the date of the first insertion and the number of subsequent revisions, if any.

18. COGNITIVE EVALUATION:

The Bayley infant scales of development should be administered by a trained psychometrician who has no prior knowledge of the treatment mode. The post-term age should be used to determine the mental

developmental index and the psychomotor developmental index. Both indices should be recorded. The raw scores are not necessary. If the Bayley score is less than 50 no MDI or PDI can be obtained. In such a case, using the same criteria for the Bayley a development quotient should be determined, i.e., the average of the mental age and the motor age each divided by the post-term age. The original Bayley forms should be sent to the Coordinating Center along with the data collection form.

19. CHEST X-RAY:

Chest x-ray should be repeated if abnormal during the interim visit. It thus will be done only on babies with chronic lung disease who have not cleared radiologically. Abnormalities that are present should be described using radiological terminology.

20. CLINICAL IMPRESSION:

This section is to record the overall impression of the clinician at this visit in regard to the respiratory system, the cardiac system and the neurologic status.

A. RESPIRATORY SYSTEM:

If chronic lung disease is present, record whether this is felt to be secondary to the neonatal disease or has developed independently (i.e., cystic fibrosis).

B. CARDIAC SYSTEM:

The cardiac system should be evaluated for evidence of right heart strain secondary to chronic lung disease.

C. NEUROLOGICAL STATUS:

The neurological status should be recorded in terms of totally normal or uncertain or abnormal. Abnormalities are major CNS

diagnoses which include hydrocephalus, cerebral palsy, and seizure disorders. Cerebral palsy is defined as persistent hypertonicity and hyperreflexia of muscle groups with associated impaired function. Diplegia refers to cerebral palsy in which the lower extremities are predominantly affected. Quadriplegia refers to cerebral palsy in which the upper extremities and trunk are predominantly affected. Hemiplegia refers to unilateral signs similar to those seen with quadriplegia (e.g., right arm and right trunk more severely affected than leg: left side normal).

Please determine the degree of handicap imposed by each defect. This evaluation is very subjective but may be defined as follows:

mild - no interference with normal life style.

moderate - normal life style possible with some help (i.e., hearing aid, CP with independent motor function but unable to run or play actively).

severe - marked interference with normal life style (i.e., blind - severe CP).

D. ~~SEIZURE DISORDER~~: HEARING IMPAIRMENT:

Indicate degree of severity.

E. ~~OTHER:~~ VISUAL IMPAIRMENT:

Specify and indicate severity.

21. DAYCARE:

Self-explanatory.

22. SHARE BEDROOM:

Self-explanatory.

23. SMOKE:

Self-explanatory.

24. CHRONIC BRONCHITIS:

Self-explanatory.