OBSTETRICAL DETERMINANTS OF NEONATAL SURVIVAL

Protocol

The National Institute of Child Health and Human Development
Maternal Fetal Medicine Units Network

Prepared by the

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October 19, 1992

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Preface

Protocol Edition:

This protocol, "OBSTETRICAL DETERMINANTS OF NEONATAL SURVIVAL", is maintained by the MFMU Network's Biostatistical Coordinating Center (BCC) during the course of the study. The final version, dated October 19, 1992, was approved by the MFMU Network Steering Committee on October 19, 1992. Any subsequent changes, with the reasons for the changes and the dates of formal approval by the Steering Committee and the Network Advisory Board, are summarized below.

Protocol Amendments

None.

1 Introduction

1.1 Study Abstract

In this pilot observational study, the effectiveness of using obstetrical factors to predict the survival of extremely low birth weight infants will be examined. The attitude of the physician, and the estimations of gestational age and fetal weight during the pregnancy are among the factors to be examined. These factors will be evaluated both individually and in combination. In addition, the effectiveness of using these factors to predict neonatal morbidity will be assessed. Extremely low birth weight infants born at participating MFMU Network clinical centers will be studied. All infants born weighing 1,000 grams or less will be screened during a one year enrollment period. Eligible infants will be followed until the earlier of hospital discharge or 120 days of life.

1.2 Objectives

The primary objective of this study is to gather data needed to design more definitive studies in predicting the survival of extremely low birth weight infants. Various obstetrical factors will be examined to assess which can increase the obstetrician's ability to predict neonatal survival. The secondary objective of this study is to determine if these factors can be useful in predicting neonatal morbidity.

1.3 Purpose of the Study Protocol

This protocol describes the background, design, and organization of the study, and may be viewed as a written agreement between the study investigators. It is reviewed by the Network Advisory Board and approved by the Steering Committee and the Institutional Review Board of each clinical center before recruitment begins. Any changes to the protocol during the study require approval of the Steering Committee and review by the Advisory Board. A manual of operations supplements the protocol with detailed specifications of the study procedures.

2 Background of the Study

2.1 Introduction

Determining neonatal prognosis for the severely premature fetus is difficult but important in counseling and guiding obstetrical management. Although maturity appears to be a more important factor than birth weight, inconsistencies and current limitations in methodology have made survival rates based on gestational age subject to an inordinate degree of variation. The obstetrician frequently relies on survival rates based on birth weight; error in estimating fetal weight limits the confidence regarding prognosis before delivery. Previous studies and pilot data indicate that underestimating fetal weight influences obstetrical management and is associated with higher perinatal mortality rates. Survival rates for infants weighing less than 800 grams have improved in recent years and current data based on information available during labor is extremely limited. The primary purpose of this study is to gather and compare the accuracy of prognostic factors available to the obstetrician when formulating management. Secondary goals are to investigate how attitudes of the obstetrician and pediatrician may influence prognosis and to develop a multivariate model for neonatal survival based on obstetrical factors.

2.2 Epidemiology of Extremely Low Birth Weight Deliveries

1) Frequency

Extremely low birth weight (ELBW, $\leq$ 1,000 grams) infants occur in less than 1% of the overall population [1,2,3]. In regional centers, ELBW infants typically represent 1.5-2.0% of inborn births. This is attributable to referral of high risk mothers before or during labor, as well as caring for high proportions of black and economically disadvantaged women who have ELBW infants twice as frequently as the remainder of the population. Within the ELBW group, the weight distribution is fairly uniform [1,2].

2) Neonatal Mortality

Despite the relative infrequency, up to 50% of mortality among structurally normal infants occurs in this group [1]. The current approximate survival rates of ELBW infants are 60% overall, ranging from 10% below 600 grams to 80% above 900 grams [1,2,4,5,6]. It should be noted these figures are based on studies from inborn babies at large referral centers. Several studies indicate the chances for survival are enhanced by delivery at a tertiary level center [3,7].

The primary outcome measure for this study will be survival to time of discharge from the hospital or 120 days, whichever comes first. Among ELBW infants, neonatal survival (28 days) is a poor measure of long-term survival due to high postneonatal mortality rates. However, most of the postneonatal mortalities in this group occur while the infant is still hospitalized. Obtaining infant mortality rates (one year) would require tracking information, informed consent, eight additional months to generate the first final data, and significantly more expense.

3) Neonatal Morbidity

There have been major improvements in morbidity as well as mortality of ELBW infants in recent years. Nonetheless, the tendency to have disproportionate morbidity among the smallest surviving infants has persisted over the years. ELBW infants are at increased risk for: long-term oxygen dependence; significant intraventricular hemorrhage, requiring surgery for necrotizing enterocolitis or patent ductus arteriosus;

developmental delay; and permanent neurological deficits including cerebral palsy and severe mental retardation [4,5,8,9,10,11,12]. About 30% of ELBW infants suffer a significant permanent handicap [1]. In this era of limited economic resources, it has been questioned whether aggressive management of the smallest of the ELBW group is the most cost effective use of available funds. The resulting ethical dilemma has not been resolved. On the positive side, several studies indicate that improved survival of ELBW infants has not resulted in increased population frequencies of these morbidities [4,9,12]. This appears to be due to the relative infrequency of ELBW birth and reductions in the risks of morbidity among slightly larger infants.

Due to the high rate of permanent morbidity suffered by ELBW infants, survival alone is inadequate to judge success. "Intact survival" free from significant permanent handicaps has gained increasing acceptance as a preferable outcome measure. Obtaining this information requires long-term developmental assessment beyond the scope of this study. The items on the final outcome form consist of major morbidities, most of which have significant associations with permanent handicaps. Medical morbidity in the mother must also be considered; in addition to discomfort and prolonged hospitalization, cesarean birth is associated with higher frequencies of infectious complications, hemorrhage, and anemia. When performed for the ELBW infant, it frequently requires a classical incision that commits the mother to abdominal delivery in subsequent pregnancies, compounding the immediate morbidity. In addition to medical considerations, an ELBW birth results in potentially serious emotional and economic costs. The duration of hospitalization may be correlated with these latter concerns.

4) Multiple Gestation

Multiple gestations account for about 20% of ELBW infants [1]. Due to an increased risk for intrauterine growth retardation (IUGR), they have a slightly better birth weight specific survival rate than singletons. Twins are also at risk for mortality and morbidity due to feto-fetal transfusion. If one twin undergoes intrauterine demise late in gestation, the survivor is at increased risk for morbidity and mortality. In addition to the risk of locking during delivery, after one twin delivers, the second twin is at increased risk for abruptio placenta.

Due to a number of considerations, multiple pregnancy would require stratification from singletons and collection of a substantial amount of additional information for meaningful analysis. The estimated number of multiple gestations during the pilot study is not anticipated to be adequate for analysis. The increased complexity of this project could potentially jeopardize successful data acquisition for singletons. For these reasons, multiple pregnancies will be excluded from this study.

2.3 Obstetrical Information Used to Predict Viability

1) Last Menstrual Period

Traditionally, obstetrical dating relied primarily on the date of the last menstrual period (LMP). Current terminology, including that used in this protocol, is based on the number of completed weeks (not rounded) from the start of the LMP. Based on an assumed 28 day menstrual cycle, this is two weeks greater than the actual duration of pregnancy post conception. The estimated date of confinement (EDC) is based on 40 completed weeks (280 days) from the LMP. The regularity and interval of menses, recent use of oral contraceptives, and certainty of the date all affect the accuracy of dating by LMP. The frequency of uncertain menstrual dates varies widely in different populations and often limits the value of LMP dating in large clinic settings. Since uncertain menstrual dating is associated with a significantly increased frequency of IUGR, restricting studies to those with reliable menstrual dating introduces a bias and limits the applicability of their findings. Opinions regarding the value of dating by a reliable LMP vary. Some reports

indicate that it may approach the accuracy of ultrasound dating after the first trimester, when crown-rump length can be measured accurately [13]. LMP dating and ultrasound dating after the first trimester share a similar proportion of variance (80-85%) with independently obtained pediatric estimates of maturity using the Ballard modification of the Dubowitz examination.

2) Obstetrical Examination

Pelvic examination during the first 10 weeks of pregnancy under ideal circumstances is also believed to be a very accurate dating method. Late presentation for care, obesity, inexperience of the examiner, inability to cooperate with pelvic examination, uterine leiomyomata, and the position of the uterus can contribute to error in estimating gestational age (GA) using this technique. The combination of a reliable LMP and a consistent early pelvic examination is believed to be quite accurate and is still used as a standard to judge the accuracy of estimates based on ultrasound measurements [13]. The accuracy of obstetrical examination declines later in pregnancy, where evaluation is based on fundal height (MacDonald's Rule) and/or clinical estimate of fetal weight by palpation.

3) Pregnancy Tests

The clinical logic used for this factor is that a positive result implies pregnancy of a given duration that varies based on the type of test. Quantitative serum beta-HCG assays can be positive three weeks after the LMP. Qualitative serum or urine beta-HCG specific tests can be positive four weeks after the LMP. Less expensive urine tests usually employed in clinic settings imply a gestational age of six weeks. User reliability of home pregnancy testing to date pregnancies has not yet been reported.

4) Auscultation of Fetal Heart Tones

Audible fetal heart tones can be used to assume a duration of pregnancy greater than 18-20 weeks using a fetoscope or 10-12 weeks using Doppler ultrasound. Documentation of 20 weeks since first auscultation of fetal heart tones using a fetoscope was considered adequate dating for scheduling elective repeat cesarean sections until quite recently. Many obstetricians now rely exclusively on Doppler devices. Although these findings are used clinically to guide management in some cases, their use in predicting neonatal survival of ELBW infants has not been studied.

5) Ultrasound Examination

Of frequently available measurements, crown-rump length is the most accurate in dating pregnancy. It is reported to be accurate to within seven days. The next most accurate predictor is femur length, followed closely by biparietal diameter (BPD) or head circumference. Early in the second trimester, accuracy is said to be within 10 days; late in the second trimester, two week accuracy is reported. Some authors have advocated head circumference as the preferable head measurement to minimize the effect of variation in the shape of the fetal head related to position or molding. Head measurements have the potential advantage of being relatively spared from changes due to IUGR. In contrast, head growth appears to be particularly susceptible to the effects of alcohol and cocaine abuse during pregnancy, factors which may reduce the likelihood of neonatal survival. Abdominal circumference is the least accurate of ultrasound measurements. The two frequently used techniques for this measurement, direct or calculation from average diameter, give significantly different results. However, when used with the appropriate standard curve, no clear advantage for one of these methods has been demonstrated. The value of using multiple ultrasound measurements or repeated testing to determine gestational age remains controversial. Ultrasound estimates of fetal weight

(EFW) are calculated from abdominal and either femur or head measurements, or on all three measurements. The most accurate formulas weight abdominal measurements more than the other measurements [14]. Using estimated fetal weight as a primary guide to management gives a paradoxical emphasis on the least accurate ultrasound dating predictor.

2.4 Physician Attitude

In 1979, Paul et al. [15] reported that underestimating the fetal weight to be 1,000 grams or less was associated with fewer cesareans and higher perinatal mortality rates. Survival has improved since that time, but a similar pattern was noted in a pilot study described below for infants weighing less than 800 grams. These reports suggest the hypothesis that the obstetrician's impression of potential viability can alter the likelihood of survival by affecting management of labor and delivery. The frequency of neonatal intubation has been used to reflect the attitudes of pediatricians and their management approach to ELBW infants [2,5]. Early mortality was closely related to the frequency of intubation. Although injudicious use of aggressive resuscitative efforts does not appear to have increased long-term survival, the pediatrician's impression of potential viability clearly has an immediate effect on the outcome [5,6]. Physician's attitudes can often be surmised indirectly from interventions, but in many cases cannot be determined from medical records. The impact of physician's attitudes have not been studied directly.

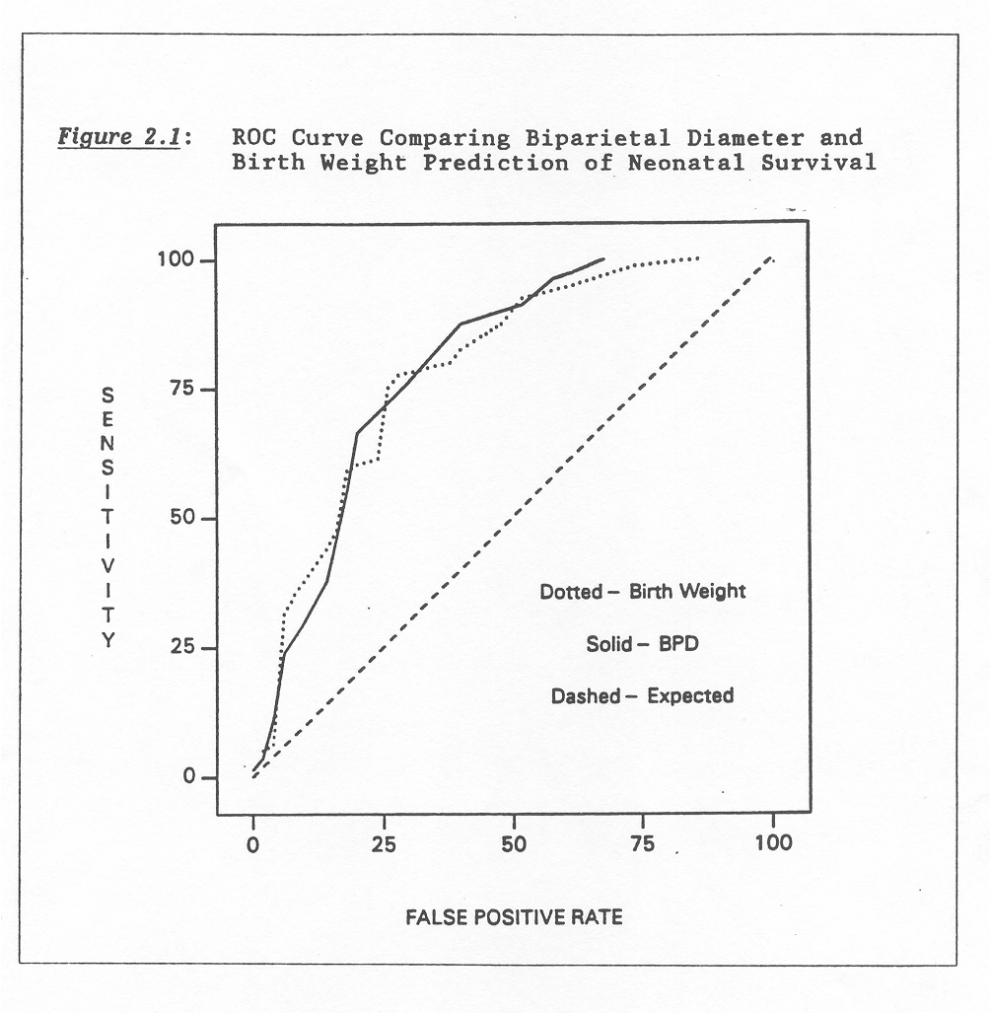
2.5 Other Factors Influencing Survival

Demographic factors such as maternal age, race, education, and family income have been related to neonatal and infant mortality rates. Since it is the most common cause of death among ELBW infants, altering the frequency or severity of respiratory disease can be expected to influence the likelihood of survival [2]. Numerous studies indicate that antenatal administration of steroids and neonatal surfactant therapy decrease the risks of respiratory disease and mortality [16,17,18,19,20]. Ruptured membranes, chronic hypertension, severe preeclampsia, narcotics addiction, use of beta-mimetic tocolytics, and labor have all been reported to accelerate pulmonary maturation; diabetes has been reported to delay this process. Clear relationships between these factors and survival of ELBW infants have not been established, but studies specific to this group have been limited. Overall, intrapartum antibiotics have been demonstrated to reduce mortality when used to treat beta-Streptococcal colonization's or chorioamnionitis; information specific to the ELBW group is not available.

2.6 Pilot Data

A preliminary retrospective investigation examining some of the obstetrical determinants of neonatal survival was performed in preparation for this protocol. Study was limited to 130 singleton liveborn infants having birth weights of 500-1,000 grams and complete ultrasound examinations within 3 days of delivery. Eighty infants survived; 50 died. For purposes of comparison, estimated fetal weight, biparietal diameter, femur, birth weight, and pediatric estimate of gestational age were evaluated as screening tests for neonatal survival using receiver-operator characteristic (ROC) curves. In this model, sensitivity and false positive rates were calculated using each value of every measurement as a cut point to predict survival. Visual inspection of the ROC curves indicated that biparietal diameter was the best single predictor. Figure 2.1 illustrates the ROC curve comparison of biparietal diameter and actual birth weight in predicting neonatal survival. Among infants < 800 grams, discriminant function analysis revealed that cesarean birth was associated with a higher survival rate, and that underestimation of fetal weight was linked with a lower cesarean rate and a worse prognosis. Irrespective of controlling for route of delivery, biparietal diameter did as well as actual birth weight and all other variables in predicting survival. Although the sample size was

sufficient for preliminary analysis of a few predictors, it was inadequate to make definitive comparisons or prognostic tables.



3 Study Design

3.1 Design Summary

This pilot study is an observational study of extremely low birth weight infants born at participating MFMU Network clinical centers. During a one year enrollment period, all infants born weighing 1,000 grams or less will be screened for the study. Data on eligible infants will be collected at birth and at the earlier of hospital discharge or 120 days of life. All data will come from patient charts and physicians. The mother will not be contacted for information. To insure uniformity in reporting criteria and to obtain information regarding physician's attitudes, labor and delivery data will be collected within one working day from the baby's birth.

Because currently available data is insufficient to design a more definitive study, this preliminary study was planned. A one year and eight month study was chosen because obtaining the primary outcome measure entails a substantial delay from entry into the study, and although infants weighing 1,000 grams or less account for a large proportion of neonatal mortality and morbidity, they represent less than 2% of the obstetrical population.

The study procedures will be conducted in a uniform manner throughout the MFMU Network center sites. Appendix A summarizes the key design features.

3.2 Inclusion Criteria

All infants born in participating centers weighing 1,000 grams or less are to be studied unless specifically excluded. The exclusion criteria are listed in the section that follows.

3.3 Exclusion Criteria

1) Infants who were part of a multiple pregnancy.
2) Infants who were delivered prior to admission to the labor and delivery unit or in a location poorly equipped to resuscitate a neonate.
3) Mothers who were diagnosed on admission to the labor and and delivery unit with an intrauterine fetal death.
4) Infants whose best obstetrical estimated gestational age at birth was less than 20 weeks, 0 days.
5) Fetuses resulting from induced abortions.

3.4 Study Outcomes

Outcome data will be collected for every infant enrolled in the study.

3.4.1 Primary Outcome

The primary outcome for this study is survival to the earlier of hospital discharge or 120 days of life.

3.4.2 Secondary Outcome

The secondary outcome measurement is neonatal morbidity. Each infant who survives the first 120 days of life free from significant permanent handicaps will be considered an "intact survivor". Conditions that will

be used in this study to determine "intact survival" include: Grade III or IV retinopathy of prematurity, necrotizing enterocolitis requiring surgery, Grade III or IV CNS hemorrhage, seizures, oxygen dependence, and neurological abnormalities.

4 Study Procedures

4.1 Screening

The labor and delivery log book will be screened every working day to identify all birth weights 1,000 grams or less and all unrecorded birth weights. Unrecorded birth weights will be determined from the NICU log book, the mother's chart, or the pathology record. A screening log will be made of all extremely low birth weight infants. All infants listed in the screening log must be enrolled in this study or have the reason for their exclusion noted in this log.

4.2 Baseline Data Form MO02

Within one working day of delivery, a baseline data form should be completed for each eligible infant. This will ensure ready availability of the mother's hospital chart and accurate recall of the obstetrician's and pediatrician's attitudes. All of the information needed to complete this form should come from the patient's chart. In cases where the physician's attitude is not clear from the chart, the physician who actually determined management should be contacted. If this is unclear from the record, the most senior physician physically present at birth should be asked. The mother should not be contacted to provide information.

4.3 Active Enrollment List

As part of the network microcomputer software, a report will be available that generates a list of all baseline forms not yet having a corresponding final outcome form. This list will be used to check hospital computer systems and/or nursery records on a weekly basis to determine if the baby is still hospitalized. It will also identify babies reaching 120 days since delivery.

4.4 Transferred Infants

In case of transfer to another hospital, it is important to maintain weekly phone contact with the receiving institution to determine the infant's status and obtain information for the final outcome form.

Infants transferred to a chronic care facility should be considered discharged from the hospital. Their final outcome form should be completed.

4.5 Final Outcome Form MO03

The final outcome form should be filled out and entered into the network microcomputer within two weeks of the earlier of hospital discharge or 120 days of life.

4.6 Operational Requirements

Prior to the start of the study, each participating clinical center will be asked to test study procedures at their institution. The purposes of the pretest are to familiarize the study staff with study procedures and logistics, and to determine whether any changes to the study design, operating procedures or data collection forms are warranted. All study personnel will be certified in study procedures, data collection procedures, forms completion and data entry before the start of the study.

5 Data Processing

5.1 Data Collection Forms

Data will be collected on three standardized forms, on which nearly all responses have been precoded. Each form is described briefly below.

- MO01 - Screening Log (completed for all infants weighing 1,000 grams or less, or with an unrecorded birth weight).
- MO02 - Baseline Data Form (includes maternal baseline data, pregnancy events, obstetrician's attitude, and labor and delivery data).
- MO03 - Final Outcome Form (includes infant care and final status data).

5.2 Distributed Data Entry System

The microcomputer data entry system consists of a network of microcomputers, one at each clinical center and one at the Biostatistical Coordinating Center (BCC). Data entry software corresponding to the study forms will be developed and maintained by the staff of the Biostatistical Coordinating Center. Data will be entered by clinical center staff, and transmitted weekly via telecommunications link to the BCC. Detailed instructions for entering and transmitting data are provided in the MFMU Network Distributed Data Entry System Handbook (User's Manual).

5.3 Centralized Data Management System

All newly created and updated data forms are transmitted weekly from the clinical centers to the BCC where they are uploaded to the mainframe computer. They are merged with the existing database on the mainframe. The data are automatically edited on an intraform basis for missing, out of range and inconsistent values. After review at the BCC, edit printouts are returned to the center for correction or clarification on a weekly basis. At regular intervals, audits, which compare data across forms (interform), are run by the BCC on the entire database or on a specific subset of data. These audits are also submitted to the centers for corrections.

5.4 Performance Monitoring

The BCC will present regular reports to the ODNS Subcommittee and the Steering Committee. These include:

- Recruitment reports: Reports of the number of patients screened and enrolled into the study by month and by clinical center will be provided monthly to the Steering Committee. This report will include tabulations of the various reasons for exclusion.

- Quality control reports: Reports concerning the quality of data collected, amount of missing data and adherence to study protocol by clinical center, will be submitted periodically to the Steering Committee.

6 Statistical Considerations

6.1 Sample Size and Power

Assuming 1.5% of births will meet inclusion criteria, 60,000 births per year within the MFMU network, and a 30% exclusion rate, 630 baseline forms would be gathered during the year. This estimate appears to be consistent with the experience of the NICU network, which is of comparable size. It is anticipated that half of these will be 120 days or more after delivery by 10 months into the study. It seems safe to assume that about 80% of these cases will have ultrasound data as well as obstetrical and pediatric estimates of gestational age. Existing data is insufficient to determine how frequently other obstetrical variables will be available; further attempts to estimate frequencies of joint availability of multiple variables for purposes of comparison would be highly speculative. Definitive power calculations are impossible without the information to be gathered in this pilot study. One year into the study, a detailed preliminary analysis will be accomplished to develop specific hypotheses, perform definitive power analysis, and make precise duration and cost estimates. A critical appraisal of these factors and the value of information developed during the pilot study will provide a sound basis for extending, revising, or discontinuing the study.

6.2 Statistical Analysis Plan

For each of the obstetrical dating factors available in a sufficient number of cases, the accuracy of predicting survival will be compared using ROC curve analysis. A similar analysis will be performed using a composite measure of major neonatal morbidity. Logistic regression will be used to develop a preliminary multivariate predictive model. This will allow evaluation of the influence of physician's attitudes, cesarean birth, and neonatal intubation, while controlling for other significant determinants of outcome such as steroid or surfactant therapy.

7 Study Administration

7.1 Organization and Funding

The Obstetrical Determinants of Neonatal Survival study is being conducted by the Maternal Fetal Medicine Units Network. The Network is funded by the National Institute of Child Health and Human Development (NICHD) under cooperative agreements between twelve institutions - eleven clinical centers and the Biostatistical Coordinating Center (BCC). Each of the eleven clinical centers and the BCC are represented by a Principal Investigator (PI).

7.1.1 Participating Centers

The eleven clinical centers participating in this study are all part of the MFMU Network. The Principal Investigators have agreed to abide by the study protocol and to have comparable staff, facilities and equipment. The BCC is responsible for all aspects of biostatistical design, analysis and data management of the study, in addition to the interim and final statistical analyses. The BCC collaborates with the Steering Committee members in preparing publications based on the study results. The Principal Investigator of the BCC reports to the Steering and Data Monitoring and Safety Committees.

7.1.2 NICHD

In addition to its role as funding agency, the NICHD participates in the activities of the cooperative agreement. NICHD staff participate in the development of protocols and coordination of the studies conducted by the Network.

7.1.3 Network Advisory Board

Appointed by the NICHD, its members include the director of the CRMC, the NICHD Network program officers, chairpersons of the Network Steering Committees and outside experts and consultants. Its role includes assisting in the identification and prioritization of research projects and reviewing final protocols.

7.2 Committees

7.2.1 Steering Committee

This committee is comprised of fourteen members: one Principal Investigator from each of the eleven clinical centers and the Biostatistical Coordinating Center, the NICHD/CRMD/PPB Special Assistant, and the Chairman of the Steering Committee. In addition, the Center for Research for Mothers and Children, the Epidemiology and Biometry Research Program, and the Pregnancy and Perinatology Branch of NICHD are each represented by one non-voting member. The Chairman, a person independent of the participating institutions, is appointed by NICHD. The Steering Committee has the responsibility for identifying topics for network studies, designing study protocols, and monitoring study implementation, recruitment and protocol adherence. The committee receives recommendations from the Data Monitoring and Safety Committee and the Network Advisory Board. The Principal Investigator from each clinical center is responsible for ensuring the proper conduct of the trial at his or her center including: recruitment and treatment of patients as specified in the protocol, accurate data collection and the transmission of information to the Steering Committee.

7.2.1.1 Protocol Subcommittee

The Obstetrical Determinants of Neonatal Survival Subcommittee is responsible for the preparation and conduct of this study. The subcommittee will report the progress of the study to the Steering Committee.

7.2.1.2 Publications Subcommittee

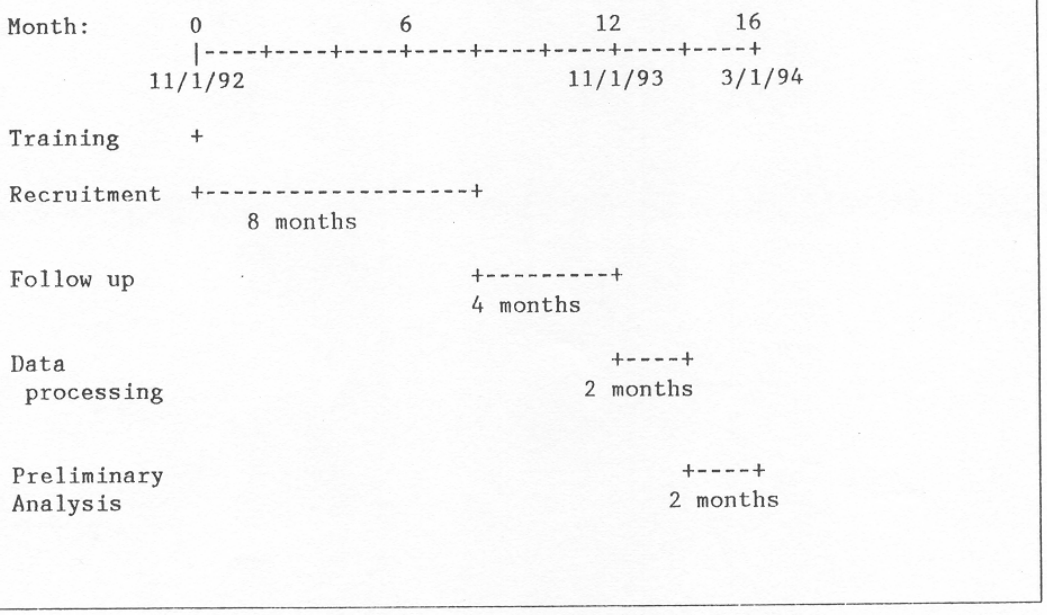
The Publications Subcommittee is a standing subcommittee of the Steering Committee. The functions of this committee are to develop publication policies and to review all manuscripts and abstracts prior to submission. The goals of this committee are fair and appropriate authorship credit and high quality publications.

8 Study Timetable

8.1 Preliminary Analysis

One year after the start of the study, a subset of the data base will be created for analysis. The subset will contain complete information on all infants who entered the study during the first eight months. Approximately four months will be required to complete data entry and analyze results (see Table 8.1).

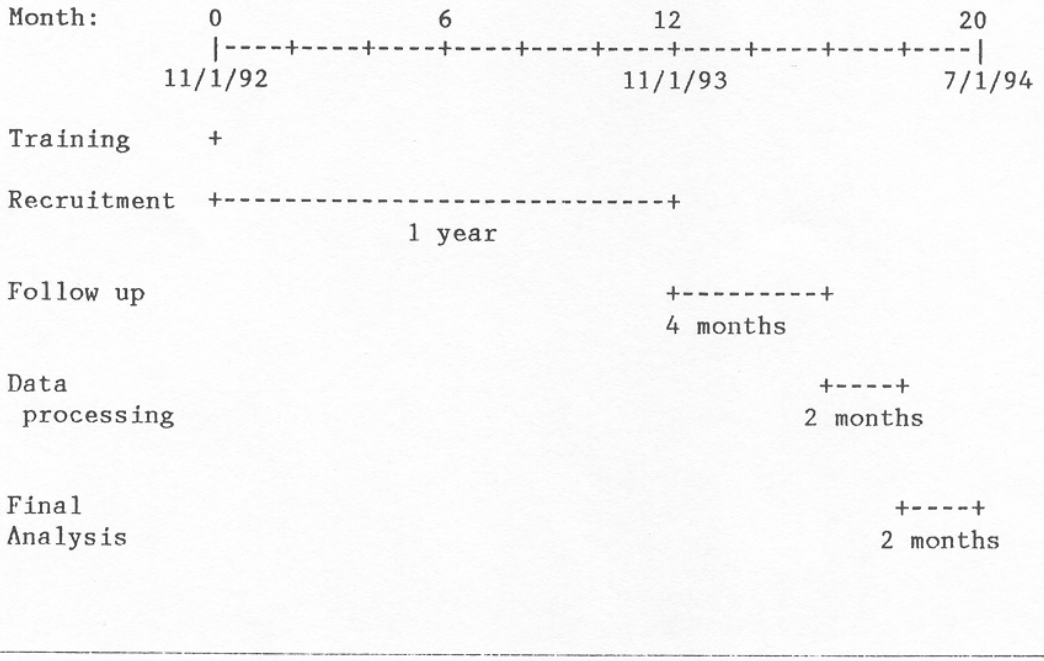
Table 8.1: Timetable of Activities for Preliminary Analysis



8.2 Final Analysis

The final analysis of the completed trial will be finished one year and eight months after the trial begins. The study will be one year and four months long, and four months will be needed for data processing and final analysis (see Table 8.2).

Table 8.2: **Timetable of Activities for Final Analysis**



Appendix A

Maternal Fetal Medicine Units Network

Obstetrical Determinants or Neonatal Survival

OBJECTIVE:

To examine the effectiveness of using obstetrical prognastic factors to predict the survival of infants born weighing 1,000 grams or less.

Organization

Clinical centers: 11 centers

Subcommittee: Dr. Bottoms (Chair)

Design

Type: Observational pilot study

Major Eligibility Criteria: All babies born weighing 1,000 grams or less are eligible for the study, with the following exceptions:

- Infants who were part of a multiple pregnancy
- Infants born before admission to the labor and delivery unit
- Mothers who were diagnosed on admission to the L&D unit with IUFD
- Infants whose estimated gestational age at birth is <20 weeks, 0 days
- Fetuses resulting from induced abortions

Sample size: Goal: 630 completed final outcome forms

Assumption:

- 60,000 births in the MFMU network
- 1.5% of births will meet inclusion criteria
- 30% exclusion rate

Scheduled Evaluations

Screening: Every working day the L&D log book will be reviewed. All eligible infants will be enrolled in the study and have a baseline data form completed.

Active Enrollment List: Every week, hospital records will be checked on all infants that have been enrolled in the study, but do not have a final outcome form completed. Final outcome forms should be filled out when an infant dies, survives 120 days, or is discharged from the hospital.

Outcome Measures

Primary: Neonatal mortality (measured by the earlier of discharge from the hospital or 120 days of survival)

Secondary: Neonatal morbidity

Timetable for Preliminary Analysis

Recruitment: 11/1/92 – 6/30/93

Follow up Period: 7/1/93 – 11/1/93

Closeout/ Analysis: 11/1/93 – 3/1/94

Timetable for Final Analysis

Recruitment: 11/1/92 – 10/31/93

Follow up Period: 11/1/93 – 3/1/94

Closeout/ Final analysis: 3/1/94 – 7/1/94

Appendix B

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