STOP-ROP STUDY
MANUAL OF PROCEDURES

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ABBREVIATIONS AND COMMONLY USED TERMS

ABG
Arterial blood gas

Anterior segment
Front section of the eye, including the lens

Aqueous humor
Watery fluid that bathes the front section of the eye

BPD
Bronchopulmonary dysplasia

CBG
Capillary blood gas

Composite
A set of clock hours with at least one missing hour, e.g. 11,12,2. A composite set may contain subsets that are internally contiguous (q.v.), but that do not touch. We discourage the use of non-contiguous, which implies that no two hours touch (e.g. 11,1,3)

Conjunctiva
Thin membrane covering the front of the eye

Contiguous
A set of clock hours with no missing hours, e.g. 11,12,1,2

Cor pulmonale
Heart disease due to pulmonary hypertension

Cornea
Front transparent part of the eye

CPAP
Continuous positive airway pressure

Cryotherapy
Freezing treatment which destroys the peripheral retina

DSMC
Data and Safety Monitoring Committee

ETT
Endotracheal tube

Fetus
A developing baby from 12 weeks gestation to birth

Fovea
Center of the macula responsible for the sharpest vision

FIO₂
Fraction of inspired oxygen

Gestation
How long the pregnancy lasts [full term is 38-42 weeks]

ICROP
International Classification of Retinopathy of Prematurity

IMV
Intermittent mechanical ventilation

Indirect ophthalmoscope
Instrument used to look through the lens of the eye and into the back of the eye

IRB
Institutional Review Board

Iris
Colored part of the eye, doughnut-shaped

Laser
Powerful beam of light that is used to destroy the peripheral retina
### ABBREVIATIONS AND COMMONLY USED TERMS - continued

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lens</td>
<td>Clear structure behind the pupil that bends the incoming light rays and focuses them onto the retina</td>
</tr>
<tr>
<td>Macula</td>
<td>Part of the retina directly behind the lens, which is responsible for central vision. The fovea is in the center of the macula.</td>
</tr>
<tr>
<td>Myopia</td>
<td>Near-sightedness</td>
</tr>
<tr>
<td>Nasal side</td>
<td>Closest to the nose</td>
</tr>
<tr>
<td>NEI</td>
<td>National Eye Institute</td>
</tr>
<tr>
<td>NICHD</td>
<td>National Institute of Child Health and Human Development</td>
</tr>
<tr>
<td>NICU</td>
<td>Neonatal Intensive Care Unit</td>
</tr>
<tr>
<td>NINR</td>
<td>National Institute of Nursing Research</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NPO</td>
<td>Nothing by Mouth</td>
</tr>
<tr>
<td>Optic disc</td>
<td>Area where optic nerve exits at the back of the eye</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>Carries impulses received by the retina to the brain for interpretation of images</td>
</tr>
<tr>
<td>Ora serrata</td>
<td>Anterior margin of the pars optica of the retina</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>The proportion of hemoglobin which is filled and carrying oxygen</td>
</tr>
<tr>
<td>PaO₂</td>
<td>Partial pressure of oxygen in arterial blood. The value can be 10-600 torr (usually 80-100 torr or mm/Hg)</td>
</tr>
<tr>
<td>PDQ</td>
<td>Parental Denver Questionnaire</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive end-expiratory pressure</td>
</tr>
<tr>
<td>Peripheral retina</td>
<td>Part of the retina closest to the front of the eye</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PIP</td>
<td>Positive inspiratory pressure</td>
</tr>
<tr>
<td>Plus disease</td>
<td>When normal blood vessels become abnormally twisted and dilated; can occur at any stage of Retinopathy of Prematurity</td>
</tr>
<tr>
<td>Posterior segment</td>
<td>Back section of the eye, behind the lens</td>
</tr>
<tr>
<td>Premature</td>
<td>Infant delivered prior to 37 weeks of gestation</td>
</tr>
<tr>
<td>Pulse Oximeter</td>
<td>Instrument used to measure arterial oxygen saturation</td>
</tr>
</tbody>
</table>
ABBREVIATIONS AND COMMONLY USED TERMS - continued

Pupil  Black hole in the center of the iris
Retina  Inner light-sensitive layer of the eye
Retinal detachment  Part or all of the light-sensitive retina comes away from the wall of the eye
Retinoscopy  Method by which a beam of light is projected into the eye to investigate, diagnose and evaluate refractive errors of the eye
RLF  Retrolental fibroplasia [old name for ROP]
Rods  Nerve cells in the retina that detect general outlines of objects and are responsible for colorless vision and night vision
ROP  Retinopathy of Prematurity
RPDQ  Revised Denver Prescreening Developmental Questionnaire
Rush Disease  An aggressive form of Retinopathy of Prematurity
SaO₂  Arterial oxygen saturation as measured by a blood gas analyzer
SpO₂  Arterial oxygen saturation as measured by a pulse oximeter
SCC  Study Center Coordinator
Sclera  Outer layer of the eye, the "white" of the eye
Scleral buckle  A "belt" that goes around the eye to prevent or treat small areas of retinal detachment
STOP-ROP  Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity
Strabismus  Crossed eyes
Temporale  Closest to the temples, or the side of the head
Vitrectomy  Surgical procedure for reattaching the retina
Vitreous humor  Gelatinous material that fills the cavity in the back of the eye and gives the eye shape
CHAPTER 1

STUDY QUESTION AND SYNOPSIS


CHAPTER 1

STUDY QUESTION AND SYNOPSIS

1.1 STATEMENT OF THE PROBLEM AND HYPOTHESIS

Retinopathy of Prematurity (ROP) continues to affect an increasing number of very low birth weight survivors from neonatal intensive care units. Cryotherapy, although helpful, is stressful, expensive, and not always successful. Basic bench research, animal model studies, and uncontrolled clinical studies suggest that the retinal hypoxia and ischemia that result from the ROP pathology and medical management of oxygen may in fact further aggravate the process. As described in Section 1.2, the study of Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) is designed to study the effectiveness of supplemental oxygen in reducing the incidence of Threshold ROP and to determine the non-ophthalmic impact and cost effectiveness of this treatment.

Additionally, chronic marginal hypoxia and hypoxic episodes among the survivors of premature birth who have chronic lung disease leads to pulmonary hypertension, and even death due to cor pulmonale. Increasing the supplemental oxygen could help to relieve the marginal hypoxia which is believed to contribute to cor pulmonale and the growth failure that these infants experience. Unfortunately, fear of precipitating vision loss from ROP leads neonatologists to restrict oxygen administration to the lowest amounts consistent with survival. If the above hypothesis proves true, it would provide data on which to safely permit more generous administration of oxygen to these infants.

1.2 SPECIFIC AIMS

1.2.1 The primary specific aim is to determine if supplemental oxygen will reduce the proportion of infants with Prethreshold ROP that advance to Threshold ROP. Infants with Prethreshold ROP in at least one eye will be randomized to receive conventional versus supplemental oxygen for at least two weeks, and the proportion in each arm of infants with one or both eyes progressing to Threshold ROP will be compared.

1.2.2 The secondary aim will be to determine the non-ophthalmic impact of this treatment. Infants’ rates of growth, pulmonary status, and hospital stay will be prospectively measured and analyzed. The Data Safety and Monitoring Committee (DSMC) will review these data along with the ophthalmic outcomes.
1.2.3 The third specific aim is to answer the question: "If supplemental oxygen is beneficial, is its use cost effective?" Data will be collected to analyze the effect of supplemental oxygen on ophthalmic and neonatal (non-ROP) outcomes. In addition, the potential increased costs of administering supplemental oxygen will be collected for cost effectiveness analysis.

1.3 ABSTRACT

Rationale: Retinopathy of Prematurity (ROP) remains a serious public health problem causing significant visual sequelae. It was estimated that 2,060 premature survivors in 1991 in the United States would be adversely affected by ROP, despite the now recognized use of Cryotherapy (estimates prior to Cryotherapy would have been 4,480, see Exhibit 2-2 in Chapter 2). Case control studies in premature infants, anecdotal reports of successful treatment of moderately severe ROP with oxygen, and studies conducted in an animal model which induced chronic (weeks-long) hypoxia by breathing 13% inspired oxygen (mean $P_xO_2 = 38$) during the model's healing process, suggest that hypoxia may be a critical factor associated with and perhaps influencing cases that progress rather than regress (see Chapter 2). This hypothesis is supported by the association of proliferative retinopathies with retinal hypoxia in other disorders such as diabetic or sickle cell retinopathy.

These data justify testing of the hypothesis that Supplemental Therapeutic Oxygen for Prethreshold ROP (STOP-ROP) will reduce, by at least one third, the number of infants with one or both eyes progressing to Threshold ROP.

Design: 880 infants who develop Prethreshold ROP (as defined by STOP-ROP, modified from the CRYO-ROP study, see section 6.1.1) will receive continuous pulse oximetry saturation monitoring and be randomly assigned to oxygen administration at one of two specified oxygen levels, "conventional" with pulse oximetry of 89-94% saturation vs "supplemental" with pulse oximetry of 96-99% saturation (further definition in section 7.1). Their ROP status will be measured and recorded prospectively, and the primary outcome variable will be the proportion of infants who progress to Threshold ROP in at least one eye by 3 months after their expected date of full term delivery. Secondary outcome measures include other ophthalmic (e.g. retinal detachment, macular ectopia) and neonatal outcomes (e.g. growth, pulmonary status, length and cost of hospital stay). The projected sample size is compatible with a 2-3 year enrollment using 20-30 centers.
1.4 POTENTIAL IMPACT OF STUDY OUTCOMES

If this clinically simple provision of controlled supplemental oxygen can reduce the number of infants who develop Threshold or worse ROP, it should also significantly reduce the annual toll of an estimated 412 infants (see Exhibit 2.2 in Chapter 2) with extremely low vision due to retinal detachments. These 412 infants, with an average 70 year lifetime, add 28,840 person-years of poor vision to the population’s morbidity each year. Of at least equal impact, however, is that if severe ROP is effectively treated by supplemental oxygen treatment, a reduction in the incidence of milder degrees of cicatricial ROP (less than retinal detachment) that now affect an estimated 2,060 infants each year may be achieved, further reducing the adverse impact of ROP in premature survivors. Infants with cicatricial ROP have severe myopia, retinal folds which cause strabismus and amblyopia, and a higher incidence of nystagmus and retinal detachments later in life. The number of infants expected to be affected has been adjusted for the predicted benefit of cryotherapy assuming it is universally available and used. The morbidity is thus reduced by about 40% over the expected morbidity without cryotherapy, although there are no long-term studies yet available on cryotherapy follow-up to assure us that the benefits will persist.

In addition to the potential benefit for ophthalmic outcomes, data from the pediatric literature support the possibility that infants given slightly higher amounts of oxygen may gain weight faster, grow faster, and be prepared for discharge from the hospital sooner. If the supplemental oxygen proves to be beneficial, or at least not harmful to the eyes, further studies beginning such treatment earlier in the hospital course would be supported. Supplemental oxygen could potentially shorten hospital stays and therefore reduce costs for the approximately 39,000 infants born each year weighing less than 1500 grams at birth.

1.5 DECISION ANALYSIS OF THE POTENTIAL COST AND EFFECTIVENESS OF THE PROPOSED TRIAL

1.5.1 Background

Formal decision analysis is quite helpful in determining a) whether a proposed clinical trial is likely to be worth pursuing, and b) in identifying supplemental data that must be collected to permit interpretation and application of the results of the trial (38). The following analyses were performed for these two purposes and in summary show two key results:

1) If supplemental oxygen is effective, the potential savings in people-years of useful vision (health status) and societal dollars would be favorable over a fairly large range of cost of treatment, although the cost of seriously prolonged hospitalizations (more than a couple of weeks) could overshadow the beneficial effects. For example, if supplemental oxygen and cryotherapy both failed to help infants with particularly severe ROP (zone 1
"rush" disease) and both salvaged vision in milder ROP with no sequelae, cryotherapy for indicated disease (approximately $1800 cost) would be preferred because it would not prolong hospitalization nearly as often, whereas supplemental oxygen potentially could prolong hospitalization in some infants for several weeks (estimated $800 per day).

2) Sensitivity analysis reveals that in addition to determining the efficacy and magnitude of the efficacy of the supplemental oxygen, the key data needed to determine whether it should be recommended for general application are a) the duration of prolonged hospitalization (if any), the costs of oxygen administration and prolonged hospitalization for the category of infants who have developed Prethreshold ROP at that time in their hospitalization (some have been discharged home), the costs of cryotherapy, the potential differences in the costs of ophthalmic care (other than cryotherapy) for infants treated with or without cryotherapy, and the long term rates of successful outcome with cryotherapy. The estimates of cost of successful outcome with cryotherapy as the only treatment have been performed by Javitt and associates (39) and those estimates will be taken into account in a more refined decision tree.

Data on the neurodevelopmental outcome of infants of this birth weight will also be needed and these are being collected by the proposed Phase III portion of the Cryotherapy for ROP study.

1.5.2 Question 1: If supplemental oxygen were to prove totally effective in preventing progression of ROP, would it be worth using?

A relatively simple decision tree will serve our purpose here. From the Natural History Cohort of infants reported in the Cryotherapy trial, we know that among infants with Prethreshold ROP, one third will progress to Threshold and two thirds will regress (heal). Of those eyes that reach Threshold, about half will proceed to poor outcomes without cryotherapy and about one quarter if cryotherapy is used. Therefore, the maximal possible benefit that supplemental oxygen could achieve would be to reduce the proportion of infants requiring cryotherapy from .33 to zero, and the proportion with adverse visual outcomes from .083 (= .33 x .25) to zero. Looked at in another way, for every 100 infants who have prethreshold ROP, all 100 would have to be treated with supplemental oxygen for the sake of the 33 who would otherwise receive cryotherapy of whom 8 would lose vision despite cryotherapy. The costs of treating 92 infants who will recover for the 8 infants who would have vision loss (1/3 cryo x 1/4 unfavorable) says that the cost of the supplemental oxygen may not be worth it, even if effective. It will depend on the relative cost.

But the first question is answered: It appears worthwhile to raise the amount of oxygen given 100 infants for a few days or weeks in order to preserve vision in eight infants and avoid cryotherapy in 33 infants (assuming here 100% efficacy and no side
effects). In a more complete analysis the choice will depend on a number of factors, most especially cost (Section 1.5.3).

1.5.3 Question 2: What factors are important in determining the cost/benefit outcomes of Supplemental Oxygen for Prethreshold ROP (STOP-ROP)?

To develop a useful list of desired information, it is necessary to construct a logical "tree" of possible outcomes of different decisions and then to determine what information is missing in order to know which branch of the tree is the preferred strategy. Exhibit 1-1 is the Decision Tree that we used for this analysis. The possibilities for added branches in such a tree are nearly endless, and we have necessarily made some choices about what issues to include or exclude for the present.

1.5.3.1 Assigning probabilities to decision and outcome paths in a decision tree. assumptions and facts. The tree starts at the left with the identified condition of Prethreshold ROP. Two choices (branches on the tree) are offered, either follow the infant on conventional management or treat with supplemental oxygen (RxO2). The next set of branches show the initial outcomes; we will want to know how often each of them occurs (their probability).

Looking first at the follow branch, the infants may regress or progress to Threshold. From the CRYO-ROP Natural History Study (25), we know that the probability of regression is 0.67 (pRegress) and this value has been assigned to the tree there. Conversely, the probability of reaching Threshold in at least one eye is 0.33 (1-pRegress, shown on the tree as the residual or "#").

The outcomes following regression could be good in both eyes (GoodGood), good in only one eye (GoodBad) or bad in both eyes (BadBad). Based again on the study of the Natural History of ROP (25), we know that GoodBad or BadBad outcomes are rare following regressed ROP. For simplicity, an incidence of 1% has been assigned to each of these latter possibilities, although it is likely even lower. A GoodGood outcome is therefore set at a 98% frequency.

Threshold ROP can occur in either one eye (which we have assumed will be treated with cryotherapy) or both, where either one or both eyes may be treated. For the sake of analyzing this decision tree, some extrapolations have been made from the CRYO-ROP data(7). If only one eye develops Threshold ROP (20% of cases), the disease is generally milder overall, regresses fully 85% of the time without treatment, and is more responsive to cryotherapy. Therefore, the probability of a GoodGood outcome has been set even higher (0.90 for a GG_1, GoodGood Outcome after treating one eyed Threshold ROP) and it is assumed that almost all the residual of the infants on this branch would have GoodBad outcomes (0.09 the probability for GB_1, a GoodBad outcome following treatment with cryotherapy to one eyed Threshold ROP). The residual (#) is a probability of 0.01 for a BadBad outcome (BB_1) when one eye has received cryotherapy (with the other eye less severe than threshold).
EXHIBIT 1-1

DECISION TREE FOR EVALUATING STOP-ROP

Prethreshold ROP

Threshold

Both Eyes

pBoth

Cryo1/2

pCryo1/2

GB_1/2

.75
dual(Cost, UGG)

GB_1/2
dual(Cost, UGB)

Cryo2/2

GB_2/2
dual(Cost, UGG)

Cryo2/2

GB_2/2
dual(Cost, UGB)

Both Eyes

pBoth

Threshold

Both Eyes

pBoth

Threshold

GB_1
dual(Cost, UGG)

GB_1
dual(Cost, UGB)

GB_1
dual(Cost, UGB)

GB_1
dual(Cost, UGB)

GB_1
dual(Cost, UBB)

GB_1
dual(Cost, UBB)

GB_1
dual(Cost, UBB)

GB_1
dual(Cost, UBB)

GB_1
dual(Cost, UBB)

GB_1
dual(Cost, UBB)

GB_1
dual(Cost, UBB)

GB_1
dual(Cost, UBB)

GB_1
dual(Cost, UBB)

GB_1
dual(Cost, UBB)

GB_1
dual(Cost, UBB)
Legend of Abbreviations for Exhibit 1-1: When a probability appears under an outcome in the tree, this is the assigned or assumed or calculated probability for that outcome.

follow = Follow the natural development of ROP with conventional oxygen treatment
regress = ROP does not progress to threshold
GoodGood Both eyes have a favorable outcome as defined in CRYO-ROP
GoodBad One eye has a favorable outcome and the other an unfavorable outcome
BadBad Both eyes have an unfavorable outcome as defined by CRYO-ROP
Threshold Threshold ROP as defined in CRYO-ROP in at least one eye
BothEyes Threshold ROP has occurred in both eyes
CRYO1/2 Threshold in both eyes and Cryotherapy is applied to just one
GG_1/2 GoodGood outcome when both eyes had threshold ROP and one was treated
GB_1/2 GoodBad outcome when both eyes had threshold ROP and one was treated
BB_1/2 BadBad outcome when both eyes had threshold ROP and one was treated
CRYO2/2 Threshold in both eyes and Cryotherapy is applied to both
GG_2/2 GoodGood outcome when both eyes have threshold ROP and both receive cryotherapy
GB_2/2 GoodBad outcome when both eyes have threshold ROP and both receive cryotherapy
BB_2/2 BadBad outcome when both eyes have threshold ROP and both receive cryotherapy
Cryo1 Cryotherapy to the one Threshold Eye when just one eye is Threshold
GG_1 GoodGood outcome when only one eye went to Threshold and received cryotherapy
GB_1 GoodBad outcome when only one eye went to Threshold and received cryotherapy
BB_1 BadBad outcome when only one eye went to Threshold and received cryotherapy
Cost Cost is the assigned cost of treatment in the particular arm: =0 for follow, is $1800 for cryotherapy and is varied for RxO2
dual (X,Y) denotes a pair of outcomes (X,Y) associated with each endpoint
UGG the Utility (value) of having a GoodGood outcome (=100)
UGB the Utility (value) of having a GoodBad outcome (=85)
UBB the Utility (value) of having a BadBad outcome (=0)
pRegress probability that regression will occur in both eyes given conventional O₂ treatment
pRegO2 probability that regression will occur in both eyes given supplemental O₂ therapy
pGG probability that a GoodGood outcome will occur after regression
pGB probability that a GoodBad outcome will occur after regression
pBoth probability that Threshold will occur in both eyes
When both eyes reach threshold, the number of treatment possibilities proliferate (not even shown are "treat none" or "treat one and wait and then treat the second eye"), and the probabilities to assign become less well known (39, 40). The probabilities assigned here are bounded by the CRYO-ROP outcomes and adjusted according to the clinical practices that have developed since publication of that trial. The first assumption was that only 22% of infants with Threshold disease in both eyes would have cryotherapy to only one eye, and that those infants who did so probably had milder ROP and a better result from cryotherapy than those infants who had disease severe enough that their physicians treated both eyes with cryotherapy. This uncertainty, however, marks an important variable for the proposed study to collect. "What proportion of Prethreshold infants with bilateral ROP receive cryotherapy to both eyes and what are their outcomes?" The precise rates of GoodGood or GoodBad outcomes when both eyes, rather than one eye are treated is still unknown and should also be collected for comparison to the outcomes when supplemental oxygen is used.

We now go back to the other choice in the beginning and look at the possibilities in the supplemental oxygen arm (RxO2). With a little study, one can see that the tree branches are the same except that there is, at the first branch, the probability of regression if treated with oxygen (pRegO2). This is the critical variable that the study is designed to measure for a determination of effectiveness. This probability therefore, is one of the key variables to vary in sensitivity testing to determine how good the treatment would have to be to be cost effective.

Many infants with Prethreshold ROP are on oxygen already and a small change in the amount of oxygen being given has no effect on length of hospital stay or hospital charges if the need for oxygen resolves before the infant is ready for discharge home. Among 36 infants in our prospective log of Prethreshold disease, 20 (55%) were on oxygen, 13 did not need oxygen at all, and 3 (8%) would have needed oxygen to be restarted if they had been assigned to the higher oxygen target of the proposed study. Thus the magnitude of this problem is likely to be small.

1.5.3.2 Assigning values to outcomes and costs to treatments. Each possible outcome at the end of each branch in our tree is marked by a small solid square. As previously published (40), a relative value scale of 0-100 was used with BadBad=0, GoodGood=100 and GoodBad=85. These relative values provide a measure of patient well-being (utility) and the scale can be chosen arbitrarily. We selected 0 as the worst outcome (Bad-Bad outcome) and 100 as the best, consistent with previously published studies in this area.

Costs of treatment have been estimated to be $1,800 for cryotherapy (39) but are quite uncertain for STOP-ROP. At the age when STOP-ROP is started, some infants remain quite ill, are on ventilators and on oxygen; these infants are not ready for home discharge and the small change in placing them on STOP-ROP would be unlikely to have an effect on duration of hospitalization. Other infants are nearing discharge home from the hospital and the costs of treatment could vary widely if they were to have
hospitalization prolonged. Therefore, it is important to measure the actual costs and effects on hospitalization closely during the proposed trial to enable a reasonable estimate of these probabilities. Oxygen treatment of an otherwise hospitalized infant is on the order of $20-50/day, whereas if the infant must be rehospitalized or hospitalization is prolonged just for this intervention, the estimate would be closer to $800/day for a predicted 14-28 days.

1.5.3.3 Sensitivity analysis: should we do the study? To calculate the expected values of each possible choice (Follow or RxO2 in our case), the costs and utilities of each outcome are weighted by the product of all intervening probabilities appearing in the decision tree between the end-point outcome and the main trunk (Choose). These are then summed across all outcomes within each decision arm (Follow and RxO2), providing the expected value of costs and utilities for each treatment possibility. This process is called "folding back" the tree. One then compares the expected costs and outcomes of each treatment choice: if one has lower costs and better health outcomes than the other it is said to be a dominant strategy. If one has better outcomes and also increased costs, then one calculates the cost per improved outcome (cost-effectiveness comparison) and determines if that cost is sufficiently low to make it worthwhile using the better (but more expensive) strategy.

To conduct a sensitivity analysis, the decision tree is folded back repeatedly with key probabilities varied across the range of possible values while holding the rest of the tree constant. This becomes a key step in the decision to conduct the trial itself: If one strategy dominates the other over all possible ranges of unknown variables, then there is no need to conduct the trial. If neither strategy is dominant, then this sensitivity analysis focuses attention on the variables on which the decision depends most crucially, and we can focus data-gathering efforts on those variables (38).

1.5.3.4 Results of Sensitivity Analysis

Exhibit 1-2 shows a graph of how the cost of treatment and a range of possible effectiveness of the supplemental oxygen influence the added cost per bad/bad outcome prevented. In this figure, increasing the cost of supplemental oxygen treatment increases the cost per bad/bad outcome prevented for any given degree of treatment efficacy (pRegO2), and greater effectiveness of the oxygen treatment (pRegO2) reduces the cost of avoiding a bad/bad outcome for any given cost of supplemental therapy.

As treatment benefit falls below 0.67 (the area to the left of the vertical axis), the oxygen treated children fare worse and the treatment costs more. Thus, the "follow" strategy dominates the supplemental oxygen strategy. Similarly, as the added cost of supplemental therapy becomes negative (the region below the horizontal axis), then that choice becomes dominant, since it has both better health outcomes and lower cost.
EXHIBIT 1-2
COST EFFECTIVENESS ANALYSIS

Interpreting the cost effectiveness graph

For any specific cost assumed for supplemental O₂ therapy (e.g. $4,000 per patient), the associated curve shows the additional cost per bad/bad outcome prevented using STOPROP compared with waiting until ROP emerges and then using Cryotherapy. The graph shows these added costs for various assumed values of the efficacy of STOPROP, i.e. the proportion of patients in whom ROP regresses to normal. At points to the left of the vertical axis, waiting and using Cryo ("follow" therapy in the decision diagram) is a dominant strategy (better health outcomes and lower cost). At points below the horizontal axis, using supplemental oxygen (RxO₂ in the decision diagram) is the dominant strategy, because it both produces better health outcomes and reduces total cost. For points shown on the graph (i.e. those sets of values where neither strategy is dominant), one can interpret the incremental cost per bad outcome prevented as the required level of society's willingness to pay to prevent a bad outcome before using STOPROP would be preferred.
In the region graphed (better health outcomes but also higher costs for supplemental O₂ therapy), the curves show the additional cost per bad/bad outcome prevented at various values for the cost of supplemental oxygen therapy. To choose one therapy or the other in this region, one needs to decide how much society is willing to pay beyond the medical costs saved or expended in order to prevent one "statistical" bad/bad outcome. For example, if the added cost of supplemental oxygen therapy is $5000 and 75 percent of treated patients regress, then one would select supplemental oxygen therapy only if society was willing to pay at least $408,000 per bad outcome prevented. Obviously, these costs rise considerably as the additional cost of supplemental therapy increases, and only our prospective study can determine that incremental cost.

If our analysis had shown that almost the entire graph had supplemental therapy as dominant over conventional treatment irrespective of costs and irrespective of treatment efficacy, then there would be little point in performing the study (38). However, there are certainly realms where conventional therapy dominates (those where supplemental oxygen therapy has less efficacy than conventional therapy), and realms where the cost of supplemental therapy matters considerably in the decision. We believe that the added cost of supplemental therapy will largely be determined by length of stay during hospitalization of newborns on supplemental oxygen therapy vs. those on conventional therapy. Only a prospective study can provide the data on this issue, in addition to establishing the crucial efficacy parameters.

For example, if the added treatment effect is quite small (e.g., probability of regressing of 0.7), and the added costs of supplemental therapy quite large (e.g., $5,000 or more average over all treated infants—both those with prolonged hospitalization and those where it is not prolonged) then the costs per bad/bad outcome prevented could become so large as to make it an unwise decision to use supplemental therapy, even if it "worked" in a technical sense.

This analysis highlights the importance of gathering data on treatment costs as well as outcomes in order to make an informed cost-effective decision about treatment of children at risk for ROP. Thus, we will be certain to collect relevant data on cost (length of stay, physician visits, etc.) as well as the probabilities of various ROP outcomes that would be the more traditional focus of an "efficacy" study.

1.6 SYNOPSIS OF THE STUDY PROTOCOL (FOR NON-PHYSICIANS)

Retinopathy of Prematurity, or ROP, was previously called Retrolental Fibroplasia or RLF. It caused blindness in an estimated seven thousand premature infants in the United States, and ten thousand world-wide during the 1940's and 1950's when high oxygen was given to these babies in order to help them survive, not knowing that when it was continued for weeks after it was needed, it was affecting their eyes. In the late 1950's and 1960's, ROP almost disappeared after physicians learned that amounts of
oxygen, like other medications, should be carefully controlled. In the 1970's and 1980's, however, smaller and smaller premature infants began to survive more often. It became clear that when those weighing less than 2-3 pounds survive, they often have this eye problem, even if their oxygen is very carefully controlled. Much research has been done to try to solve this problem, and in 1988 the results of a study of cryotherapy, a freezing surgery, showed that the surgery on the eyes can help the babies that have severe ROP. The wild growth of blood vessels on the inside of the eye is usually stopped after cryotherapy. Surgery, however, is not always successful, and it is stressful, so that research continues on ways to stop the ROP before it gets bad enough to need cryotherapy.

Similar eye problems (proliferative retinopathies or wild overgrowth of blood vessels) develop in patients with sickle cell disease and diabetes when there is not enough oxygen getting to the retina, the sensitive part of the back of the eye that "sees." It is ironic that both too much oxygen and too little oxygen can result in such similar problems. However, that is the very idea behind this study. It is the belief of the researchers that once the eye disease starts, large parts of the retina no longer receive enough oxygen and that this oxygen starvation makes the disease get even worse. If just the right amount of increased oxygen can be given once this happens, perhaps the wild new blood vessels can be controlled, and the baby will be able to heal the retinopathy.

The research will be done on infants who already have moderately severe ROP. If their parents consent, they will be assigned by random chance (by computer) to receive conventional oxygen treatment or the supplemental oxygen treatment. About 880 infants will join the study from many different hospitals throughout the country. Those who receive supplemental oxygen may be in oxygen for more days than those in the conventional oxygen group. Eye examinations will be done by specially trained doctors each week until it is known whether the treatment was successful. If the disease gets worse instead, the infant will be offered appropriate additional therapies.
CHAPTER 2

BACKGROUND OF PROTOCOL DEVELOPMENT
AND HISTORICAL REVIEW
CHAPTER 2

BACKGROUND OF PROTOCOL DEVELOPMENT AND HISTORICAL REVIEW

Current cryotherapy for severe Retinopathy of Prematurity (ROP) is time consuming, stressful, and not always successful, and the incidence of long-term complications is unknown. Therefore, investigators continue to seek alternatives to arrest the progress of ROP before it requires cryotherapy.

2.1 THE HISTORY OF CASE CONTROL STUDIES IN HUMANS

Retinopathy of Prematurity (ROP) is a neovascular disorder affecting the retina of those infants with an immature, incompletely vascularized retina. Its key pathologic change, retinal neovascularization, has several features in common with other proliferative retinopathies such as diabetic and sickle cell retinopathy. Each of these has apparent local ischemia associated with the subsequent development of neovascularization. The smallest infants are most likely to develop ROP, and they are now surviving more frequently.

The survival rate of very low birth weight, premature infants has increased dramatically during the past four decades. During the original epidemic of retrolental fibroplasia (RLF) between 1942 and 1954, only about 8% of infants weighing less than 1000 grams at birth survived (1). By 1980, survival was reported as 35% (2), by 1985 65% (3), and in 1988-89 the survival rates approached 40-80% in infants under 750 grams while those 750-1000 grams survive >90% of the time (4). Exhibit 2-1 illustrates the change in survival curves by year, based on data from the University of Rochester, and is typical of an Intensive Care Nursery that has been using surfactant since 1983.

With this improvement in neonatal care, there has been a commensurate resurgence in the incidence of RLF, now known as Retinopathy of Prematurity (ROP). In 1979, it was estimated that annually more than 2,100 infants in the United States would be affected by the cicatricial changes of ROP. Applying those estimates to today’s survival rates, the number is closer to 4,400 without cryotherapy or 2,060 with universally available cryotherapy (see Exhibit 2-2) (2,7,25,37). At their mildest, these cicatricial (or scarring) effects of ROP are associated with high myopia and have few other immediate visual effects, but do predispose to a greater risk of retinal detachment and permanent visual loss as young adults. More moderate degrees of cicatricial ROP can result not only in higher risks of retinal detachment, but also in high myopia, strabismus and retinal distortions causing subnormal vision. At their worst, the cicatricial effects of ROP result in partial or total retinal detachment and permanent blindness beginning during infancy.
EXHIBIT 2-1

BIRTH WEIGHT SPECIFIC SURVIVAL, UNIVERSITY OF ROCHESTER

Birth Weight Ranges

- 500-749 gm*
- 750-999 gm
- 1000-1249 gm
- 1250-1499 gm
- 1500-1999 gm

Infants surviving through discharge

* The instability of < 750 g curve is due to the small numbers (n = 10-20) in any one year.
The number of premature infants born in 1979 within the United States who are blind due to ROP is estimated to be 550 (2). Utilizing 1981 survival data, it is estimated that blindness due to ROP would affect 770 infants if cryotherapy were not available. The availability of cryotherapy reduces this number to 412 (Exhibit 2-2). A recent population-based study in British Columbia (6,42) supports estimated rates of blindness due to ROP of 0.5% for survivors who were 1.0-1.5 kg at birth, and 5% for survivors less than 1 kg at birth. Although the incidence of ROP-induced visual loss should be reduced by utilization of cryotherapy (7,41,43); it is anticipated that the absolute number of affected newborns will continue to increase due to the improved survival of the very low birth weight and most susceptible infants (6,37,42). The impact of ROP in the 1970's and 1980's parallels in absolute numbers the Retrolental Fibroplasia (RLF) epidemic that occurred in the 1940's and 1950's, when an estimated 7,000 newborns were afflicted with blindness during a ten year period (1).

Technological and pharmacological advances continue to increase survival rates of premature infants and will likely result in a net increased incidence of visual loss from ROP. Although cryotherapy may moderate this incidence, it is important that new treatment modalities be developed.

Therapy for ROP has been divided into two approaches: one to attempt to prevent the disease, and the other to interrupt the disease once it starts. Preventive therapy has primarily focused on the management of blood oxygen levels. This is based on the discovery in the early 1950's of a causal relationship between ROP and prolonged administration (4 weeks) of high supplemental oxygen, regardless of oxygen need (9). However, even the best possible oxygen monitoring and control of the 1980's and 1990's has not prevented ROP (5). The use of antioxidants to prevent ROP has also been disappointing (10). Cryotherapy, an interdictive treatment once ROP is established, has been shown to reduce the incidence of visual loss (7,41,43), and is now considered to be standard for treatment of advanced ROP. The current proposal addresses therapy to interrupt the disease process when a milder stage of ROP is present. Supplemental oxygen will be utilized in an attempt to stop progression of moderately advanced ROP, thus reducing the number of infants requiring cryotherapy.

The pathophysiology of ROP is not fully understood, but we believe that it begins with damage to the delicate developing retinal capillaries (perhaps from asphyxia, shock, cold stress, acidosis or prolonged hyperoxia). It takes weeks to months for the damage to heal and that process, revascularization, is what we see as the active retinopathy. If revascularization is complete and orderly, ROP is said to have regressed. If the healing process is disorderly and progresses to retinal scars, folds or detachment, it is called cicatrical ROP and causes serious visual impairment.

Several case control studies have observed that among infants at equal risk for ROP (based on gestational age and birth weight) those infants who develop severe ROP have more complicated hospital courses, lower overall arterial oxygenation levels and more
### Exhibit 2-2

**Basis of Predicting – Estimates of ROP Morbidity**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimated births in a year</strong></td>
<td>3.4 million</td>
<td>3.8 million</td>
<td>4.1 million</td>
<td>4.1 million</td>
</tr>
<tr>
<td><strong>1.86% multiple</strong></td>
<td>63,240</td>
<td>70,680</td>
<td>76,260</td>
<td>76,260</td>
</tr>
<tr>
<td><strong>54% of multiple &lt;2.5kg</strong></td>
<td>34,150</td>
<td>38,167</td>
<td>41,180</td>
<td>41,180</td>
</tr>
<tr>
<td><strong>98.14% singletons</strong></td>
<td>3,336,760</td>
<td>3,729,320</td>
<td>4,023,740</td>
<td>4,023,740</td>
</tr>
<tr>
<td><strong>For 1.0–1.5kg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>0.52% of singletons</strong></td>
<td>17,351</td>
<td>19,392</td>
<td>20,923</td>
<td>20,923</td>
</tr>
<tr>
<td><strong>8% of multiples &lt;2.5kg</strong></td>
<td>2,732</td>
<td>3,053</td>
<td>3,294</td>
<td>3,294</td>
</tr>
<tr>
<td><strong>total births 1–1.5kg</strong></td>
<td>20,083</td>
<td>22,445</td>
<td>24,217</td>
<td>24,217</td>
</tr>
<tr>
<td><strong>% survival</strong></td>
<td>81%</td>
<td>95%</td>
<td>96%</td>
<td>95%(^b)</td>
</tr>
<tr>
<td><strong># of survivors</strong></td>
<td>16,267</td>
<td>21,323</td>
<td>23,248</td>
<td>23,006</td>
</tr>
<tr>
<td><strong>2.2% cicatricial</strong></td>
<td>358</td>
<td>469</td>
<td>511</td>
<td>425(^c)</td>
</tr>
<tr>
<td><strong>0.5% blind</strong></td>
<td>81</td>
<td>107</td>
<td>116</td>
<td>85(^c)</td>
</tr>
<tr>
<td><strong>For&lt;1.0kg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>0.43% of singletons</strong></td>
<td>14,620</td>
<td>16,340</td>
<td>17,630</td>
<td>17,630</td>
</tr>
<tr>
<td><strong>6.6% of multiples &lt;2.5kg</strong></td>
<td>2,253</td>
<td>2,519</td>
<td>2,717</td>
<td>2,717</td>
</tr>
<tr>
<td><strong>total births &lt;1kg</strong></td>
<td>16,873</td>
<td>18,859</td>
<td>20,348</td>
<td>20,348</td>
</tr>
<tr>
<td><strong>% survival</strong></td>
<td>35%</td>
<td>60%</td>
<td>65%</td>
<td>70%(^b)</td>
</tr>
<tr>
<td><strong># of survivors</strong></td>
<td>5,905</td>
<td>11,312</td>
<td>13,226</td>
<td>14,243</td>
</tr>
<tr>
<td><strong>30% cicatricial</strong></td>
<td>1,771</td>
<td>3,393</td>
<td>3,968</td>
<td>1,635(^c)</td>
</tr>
<tr>
<td><strong>5% blind</strong></td>
<td>(8%)472</td>
<td>566</td>
<td>661</td>
<td>327(^c)</td>
</tr>
<tr>
<td><strong>total # cicatricial</strong></td>
<td>2,129</td>
<td>3,862</td>
<td>4,479</td>
<td>2,060</td>
</tr>
<tr>
<td><strong>total # blind</strong></td>
<td>553</td>
<td>673</td>
<td>777</td>
<td>412</td>
</tr>
</tbody>
</table>

\(^a\) Phelps estimates (2)
\(^b\) Cryo-ROP Survival data (37)
\(^c\) Based on the CRYO-ROP Natural History and Cryotherapy outcome data (7,25)

---

<table>
<thead>
<tr>
<th></th>
<th>&lt;1kg</th>
<th>1-1.25kg</th>
<th>projected for 1-1.5kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n survivors</td>
<td>14,243</td>
<td>--</td>
<td>23,006 (from above)</td>
</tr>
<tr>
<td>% prethreshold/n</td>
<td>26.6%/3,788</td>
<td>7.3%</td>
<td>5%/1,150 total=4,938</td>
</tr>
<tr>
<td>% threshold/n</td>
<td>9.2%/1,310</td>
<td>2.0%</td>
<td>1.5%/345 total=1,655</td>
</tr>
<tr>
<td>[assume 1/4 of Threshold with cryotherapy to one or both eyes will be &quot;blind&quot;] % &quot;blind&quot;</td>
<td>2.3%</td>
<td>0.5%</td>
<td>0.37%</td>
</tr>
<tr>
<td>n &quot;blind&quot; for 1991</td>
<td>327</td>
<td>--</td>
<td>85 total= 412</td>
</tr>
<tr>
<td>[assume there are five times as many cicatricial as blind] n cicatricial 1991</td>
<td>1635</td>
<td>--</td>
<td>425 total=2,060</td>
</tr>
</tbody>
</table>

---

2-4
episodes of hypoxemia than those that do not develop severe ROP (12-15). Upon reflection, the clinical observation of lower oxygenation in the sickest infants is not surprising (these infants often have chronic lung disease and are receiving oxygen to treat hypoxia [see Exhibit 2-3]), and we know from the case control studies that the sicker infants are more likely to have worse ROP. Therefore, these data suggest that chronic (weeks-long) marginal hypoxia during the ROP healing process could be a factor in causing the ROP to become worse rather than regress, a hypothesis suggested by our understanding that other proliferative retinopathies such as diabetic retinopathy are associated with retinal hypoxia.

2.2 PREVIOUS REPORTS OF TREATMENT OF ROP WITH OXYGEN

Szewczyk reported his favorable clinical experience in several hundred infants with severe ROP that he treated by placing them into oxygen and then very gradually withdrawing it over weeks (16). These observations were uncontrolled, but support the possibility that the proposed hypothesis may be correct. During this time period, Bedrossian et al also were treating infants who developed severe ROP with a return to oxygen (17,18). They were conducting controlled trials of gradually weaning infants from high oxygen (50%) over several days and found fewer cases of ROP as compared to infants suddenly removed from oxygen (18). However, seven of their infants who developed what they called progressive ROP (mostly from the abruptly withdrawn group) were then placed back in 50-60% oxygen and all recovered with regression of their retinopathy. These data are also uncontrolled in regards to oxygen treatment (they were controlled as to initial withdrawal from oxygen), and the sample size is small, but they suggest that the theory deserves further investigation.

Because neonatologists currently believe that they give each infant just the amount of oxygen needed, and wean him from that therapy only very slowly as permitted and monitored with blood gases and pulse oximetry, the findings of Szewczyk, Bedrossian and colleagues have been forgotten. It is not clear why the concept of supplemental oxygen has gone untested, other than perhaps the whole issue has been avoided due to the medicolegal concerns of giving oxygen to an infant with vision threatening ROP.

Dr. Michael Gaynon, a retinal surgeon at Stanford University, reported his experience using supplemental oxygen for serious ROP, at the Annual Retina Society meeting in 1991. He found that over the year prior to changing oxygen treatment, his group had treated 29 infants with cryotherapy, but based on the developing information and discussions about STOP-ROP, he persuaded his associated Intensive Care Nurseries to change their oxygen administration practices. In the following one year, his group performed no cryotherapy procedures (19). Similarly, Dr. Maurice B. Landers III, of Sacramento, California, has experienced a drop from 12-15 cryotherapy procedures per year to none since July 1991 when the nursery he attends changed their oxygenation practices to be similar to the supplemental oxygen arm in the proposed study (personal communication).
These data are anecdotal, historically controlled and not peer reviewed; however, they are changes in the direction of benefit, and clearly point out the URGENT need to perform the proposed randomized trial as soon as possible.

2.3 THE KITTEN OXYGEN-INDUCED RETINOPATHY MODEL AND BASIC STUDIES

To explore this hypothesis before embarking on clinical trials, and to investigate potential safety issues, animal studies were first conducted in the kitten oxygen-induced-retinopathy model. The results strongly support the hypothesis that oxygenation levels can directly influence retinopathy. Hypoxemia induced by breathing 13% oxygen (mean PaO₂ = 38 torr) during the 3 week recovery process after an oxygen induced vascular injury causes the retinopathy to be significantly worse than in litter mate controls who breathed room air (21% oxygen, mean PaO₂ = 98 torr) during the recovery period (20). Next, the reverse study showed that increasing the blood PaO₂ to 120 torr (by giving 28% oxygen to animals with normal lungs) during the healing process in the kitten, resulted in a significantly less severe retinopathy (21,22).

Studies performed in cell culture also support these physiologic findings. Rosen and colleagues have grown retinal capillary endothelial cells under hypoxic (4% and 10% oxygen) conditions and found that their growth is significantly faster than the same cells grown in room air (21% O₂). Increasing the oxygen to 90% essentially stopped the growth of these cells (23). It appears that capillary endothelial cell growth is directly or indirectly controlled (at least in part) by oxygen concentration. Phelps has also shown that the rate of retinal vascularization in the healthy kitten is inversely related to the concentration of oxygen breathing (24).

The kitten oxygen-induced retinopathy, however, is not a perfect model of ROP. The animal lesion always heals without retinal detachments, and less intraretinal fibrovascular tissue develops. Therefore it is not justified to apply these promising results directly to the clinical condition. The proposed treatment of ROP with oxygen, however, is sufficiently supported to justify controlled clinical trials.

If this clinically simple provision of controlled supplemental oxygen can reduce the number of infants requiring cryotherapy procedures, it should also significantly reduce the annual toll of an estimated 440-770 infants with low vision due to retinal detachments. Affecting even more infants, however, are three less dramatic potential outcomes. First, if regression is truly enhanced by oxygen treatment, milder degrees of cicatricial ROP (milder than retinal detachment) that now affect an estimated 2,060-4,480 infants each year may be reduced, further reducing the adverse impact of ROP in premature survivors.

Secondly, if the controlled oxygen treatment levels are found to be safe in regards to ROP, neonatologists may then treat infants with chronic lung disease with higher oxygen than is currently acceptable. It is believed that higher oxygen will improve an infant's
pulmonary outcome from chronic lung disease and overall growth rates, although there remains some concern that local pulmonary oxygen toxicity could work in the reverse direction. Presently, fear of ROP forces stringent oxygen restriction upon the physicians caring for these babies, when logical clinical practice would dictate more liberal oxygen administration permitting the infants to have a larger margin of safety in their arterial PaO₂. This study has the potential to redefine those standards based on new data.

Third, and most speculatively, if marginal oxygenation is found culpable in aggravating ROP, by extension it may be that the rest of the developing CNS (retina is actually comparable to brain in many ways since it is a direct extension of the CNS) is also adversely affected. Supplemental oxygen may in fact enhance neurodevelopmental outcome.

2.4 RELATION OF VARIOUS ARTERIAL PaO₂ VALUES

Exhibit 2-3 illustrates the mean and range of arterial blood oxygen levels to be expected in premature infants cared for under various conditions and in different studies as well as the values in the animal studies described above. It also shows the values proposed for the two study groups in the STOP-ROP study. This exhibit is particularly helpful in assisting one to visualize the relative values involved.

2.5 RATIONALE

In summary, the rationale for the STOP-ROP study is that the proliferative retinopathy leading to retinal detachments is an overly vigorous response of the retinal vasculature to neuroretinal hypoxia and ischemia. The retinal vasculature is responsive to oxygen levels, and it is believed that increased oxygen may be used to down regulate the overgrowth, permitting orderly regression of the ROP.
EXHIBIT 2-3

ARTERIAL PAO₂ VALUES IN VARIOUS SUBJECTS

[scale at top and bottom for convenience]

<table>
<thead>
<tr>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>120</th>
<th>140</th>
<th>160</th>
<th>180</th>
<th>200</th>
<th>250</th>
<th>300</th>
<th>350</th>
<th>400</th>
<th>450</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial PaO₂ values (torr or mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

- Normal adult, in room air (21%)
- Normal subject breathing 80% O₂
- Oxygen levels associated with hypoxic brain damage
- Normal preterm infant, in room air
- Sick preterm infant receiving supplemental oxygen
- Proposed control group for the STOP-ROP study
- Proposed experimental group for STOP-ROP
- Calculated oxygen levels in 1953 collab. study of infants in the "routine" high oxygen group
- Lowest levels in kittens that will arrest retinal vessel growth
- Levels in kitten study: hypoxia assignment making the retinopathy worse
- Levels in kitten study: 28% oxygen assignment that proved beneficial
CHAPTER 3

STUDY DESIGN AND ORGANIZATION
CHAPTER 3

STUDY DESIGN AND ORGANIZATION

INTRODUCTION

The STOP-ROP study design is illustrated in Exhibit 3-1. The participating investigators and Study Centers in STOP-ROP collaborate through an organization designed to maintain continuity of operations and to facilitate effective communication and cooperation among Study Centers [see Appendix B]. The organizational structure of STOP-ROP is outlined in Exhibit 3-2, which describes the relationship between the primary funding agency, Study Headquarters, the Coordinating Center and participating Study Centers. The success of a multicenter endeavor depends on the cooperation of the staff in all centers to perform their tasks and responsibilities in an efficient, effective, and timely manner. The organization of a typical Study Center is shown in Exhibit 3-3. All committees involved with the execution of the STOP-ROP protocol are described within this chapter. A timeline for this project is illustrated in Exhibit 3-4.

3.1 STUDY DESIGN

The STOP-ROP study design is illustrated in Exhibit 3-1. Infants who are confirmed to have Prethreshold ROP as defined by STOP-ROP, modified from the CRYO-ROP Study (see Section 6.1.1), and to whom none of the exclusion criteria (6.1.2) apply will be randomly assigned to receive conventional oxygen therapy (7.1.2), or supplemental oxygen therapy (7.1.3). Their ROP status will be recorded prospectively, and the primary outcome variable will be the number of infants with at least one eye that progresses to Threshold ROP. Infants will be recruited from multiple Study Centers and the projected sample size (880 infants) is consistent with a 2-3 year accrual from 20-30 centers. Significant patient care and financial implications will be encountered (Sections 5.2, 5.3, 5.5) and can be justified by the potential savings from preservation of sight and the reduced utilization of surgical intervention in these patients, should supplemental oxygen prove to be effective.

3.2 ORGANIZATIONAL STRUCTURE

The primary funding agency for STOP-ROP is the National Eye Institute (NEI). STOP-ROP is additionally supported by the National Institute of Child Health and Human Development (NICHD) and the National Institute of Nursing Research (NINR). The permanent study organization consists of an Executive Committee, an Operations Committee, Technical Group, Data and Safety Monitoring Committee, and other committees designated by the Study Chair. The functional units in the STOP-ROP trial are Study Headquarters (Rochester, New York), the Coordinating Center (The EMMES Corporation, Potomac, Maryland), and the individual Study Centers. [See Exhibit 3-2.]
STUDY DESIGN OVERVIEW

EXHIBIT 3-1

Prethreshold ROP

Informed Consent

Randomization

Conventional Oxygen

Supplemental Oxygen

Progress to Threshold

Regressed ROP

3 months corrected age follow-up
* STOP-ROP is an NEI-funded study additionally supported by the National Institute for Child Health and Human Development (NICHD) and the National Institute of Nursing Research (NINR)
EXHIBIT 3-3

ORGANIZATION OF A TYPICAL STUDY CENTER

Principal Investigator  
Study Center Coordinator

Ophthalmologists  
NICU Nurses And Other Staff  
Neonatologists
EXHIBIT 3-4

STOP-ROP TIMELINE GOALS

May 1993  Study Headquarters/Coordinating Center funding

July 1993  • Select NEI Clinical Centers
          • Select Executive Committee

August 1993  • Purchase equipment
             • Select Data and Safety Monitoring Committee (DSMC) members

September 1993  • Complete and distribute draft Manual of Procedures/Forms
                 • Fund NEI Clinical Centers

October 1993  • Finalize draft MOP and forms
              • Pilot STOP-ROP forms

November 1993  • DSMC meeting
               • Finalize and distribute MOP
               • Deliver equipment to sites/initiate pre-training

December 1993  • Executive Committee and Technical Group meeting and training session
                • Site visits

January 1994  • Site visits
               • Randomization
3.2.1 National Eye Institute

The National Eye Institute (NEI), the primary funding agency for STOP-ROP, is directly accountable to higher levels of the Executive Branch, the Congress, and the public for the use of Institute funds and Institute programs. The Institute therefore has ultimate responsibility for the success of STOP-ROP and will be continually informed through its Extramural and Collaborative Program of the study's progress and will be involved in all major decisions affecting the course of the study. An NEI staff member will serve as a voting member of the STOP-ROP Executive Committee and Operations Committee, and as a non-voting member of the Data and Safety Monitoring Committee and Technical Group.

3.2.2 Executive Committee

The STOP-ROP Executive Committee assists the Study Chair in the scientific administration of this study. The Executive Committee formulates and implements all policy decisions relating to the maintenance and conduct of STOP-ROP. Protocol changes which relate to data analysis or human subject protection that are recommended by the Data and Safety Monitoring Committee are submitted to the Executive Committee for review and implementation by the Technical Group. Policy decisions which are drafted by the Executive Committee are subject to review or appeal by the Technical Group at its annual meeting.

The Executive Committee consists of the following permanent voting members:

- The Operations Committee (which consists of the Study Chair, Director and Co-Director of the Coordinating Center, Program Director from the NEI, Study Headquarters Project Director, and Coordinating Center Protocol Monitor)
- An Ophthalmologist, a Neonatologist, a Study Center Coordinator,
- Representative of the National Institute of Child Health and Human Development
- Representative of National Institute of Nursing Research
- Transitional Non-Funded Ophthalmologist Member (1 year)

Study Headquarters representatives (Study Chair, Project Director), share one vote between them, as do Coordinating Center representatives (Director, Co-Director and Protocol Monitor of Coordinating Center).

The Executive Committee consists of the following rotating (2 year term) voting members:

- Neonatologist from NEI funded center
- Ophthalmologist from NEI funded center
- Neonatologist from NICHD funded center
- Ophthalmologist from NICHD funded center
- Chair, SCC Group (first representative selected by Operations Committee, subsequent representatives are selected by elections held by the SCC group)
- Chair-Elect, SCC Group
- NICU Registered Nurse (selected by SCC group)

The Chair and Chair-Elect of the SCC Group share one vote.

The Study Chair, at her discretion, may appoint additional voting or non-voting members for 1 year renewable terms. These will include representatives from Alternative Funded Centers.

The functions of the Executive Committee include:

A. Train and certify Study Center Ophthalmologists, Neonatologists and Coordinators.

B. Certify Study Centers for participation in the study

C. Recommend to the Technical Group such changes or modifications in the specifications of treatment techniques as may be necessary or desirable

D. Give approval for major changes in the Manual of Procedures

E. Review and approve all ancillary studies

F. Through sub-committees and individuals, advise and assist the Coordinating Center on operational matters

G. Resolve operating problems brought to the Executive Committee by Investigators, the Coordinating Center, or Headquarters

H. Monitor the performance of all Study Centers. In this regard the committee will utilize the information provided by the Coordinating Center and site visits to evaluate the quality of data collected by the individual centers, as well as their adherence to protocol. As needed, the Executive Committee will schedule problem-solving visits to appropriate participants. Any center that is behind schedule in meeting its recruitment goals or who fails to otherwise adhere to protocol will be reviewed by the Executive Committee as to whether that center should continue to participate in the study.

I. Ensure enforcement of the editorial policies outlined in Chapter 4

J. Appoint subcommittees as necessary.

The Executive Committee meets at least on an annual basis before the Technical Group. Additional meetings may be called by the Study Chair.
3.2.3 Operations Committee

The Operations Committee is the operational arm of the STOP-ROP Executive Committee. The Committee:

- Assists the participating units in the performance of their duties
- Monitors the performance of these units in accordance with the STOP-ROP protocol
- Evaluates the efficiency and ability of the units to meet the needs of the study as defined by the protocol, the Study Chair, the Executive Committee, and the Data and Safety Monitoring Committee
- Reviews chapters of the Manual of Procedures, study forms, minutes, newsletters, and other materials prior to distribution

The members of the committee are:

- Study Chair
- Director, Coordinating Center
- Co-Director, Coordinating Center
- Program Director, NEI
- One or more Principal Investigators designated by the Study Chair
- Protocol Monitor, Coordinating Center
- Project Director, Study Headquarters

The Operations Committee reviews the activities of all Study Centers either by direct contact or from reports of groups responsible for monitoring specific aspects of study activities. Members of the Operations Committee meet or confer on the phone frequently, and usually at least once a month.

If the performance of a Study Center is unsatisfactory, the Operations Committee acts to remedy the situation. If no improvement in performance is noted, the committee may recommend that the Executive Committee consider further action.

3.2.4 Technical Group

The Technical Group is composed of all Study Centers participating in the STOP-ROP protocol. The functional voting members of this group are the Principal Investigators from each Study Center, Study Center Coordinators, Study Chair, Study Headquarters Project Director, and the Director and Protocol Monitor of the Coordinating Center. Staff members from the NEI, NICHD, or NINR may attend the Technical Group as non-voting members.

The Technical Group will meet at least annually to review progress of the study, disseminate information, and to discuss problems encountered in execution of the protocol. Face-to-face discussion of study activities and the opportunity to interact contribute to development of rapport among members of the multicenter clinical trials. Technical Group meetings are open, and all members of the study are invited to attend. Funding is provided
for three people annually (the Principal Investigator, the Study Center Coordinator, and one other physician) with the exception of the first meeting which will be held in conjunction with a Training Session. At this meeting, a Neonatologist, Ophthalmologist, Study Center Coordinator and NICU Nurse will be funded to attend.

The Technical Group reviews all decisions of the Executive Committee concerning Study Center procedures. The Principal Investigator and at least one Study Center Coordinator or their designees from each Study Center must attend all meetings.

3.2.5 Coordinators' Group

The voting members of this group are the Study Center Coordinators from each Study Center, the Protocol Monitor from the Coordinating Center, and the Project Director from Study Headquarters. The group, which meets at least annually in conjunction with meetings of the Technical Group, is responsible for providing information to the Study Chair about logistical aspects of the study protocol and procedures as they relate to each Study Center. The Chair of the Coordinators Group, a Coordinator elected by the Study Center Coordinators, is responsible for preparing the agenda for the meeting based on comments solicited by the group and consultation with the Operations Committee. The Chair of this committee serves a 1-year term and is a voting member of the STOP-ROP Executive Committee. The Chair is also responsible for selection of a NICU nurse to be represented on the Executive Committee. The Operations Committee reviews and comments on the draft agenda and materials prepared by the Coordinators Group.

Elections for the Chair are conducted annually during the Coordinators Group meeting, with each Study Center having one vote. The person elected serves as the Chair-elect for the next year. He or she assists the Chair during that year, and serves as Chair in the following year.

3.2.6 Data and Safety Monitoring Committee (DSMC)

The responsibility for reviewing the ethical conduct of the study and for monitoring reports for evidence of adverse or beneficial treatment effects is assigned to the Data and Safety Monitoring Committee. The DSMC is also responsible for providing advice to the Executive Committee and to the NEI on operational issues that would improve the quality of the trial. Results of reviews will not be available to the participating ophthalmologists, neonatologists, or other study members who are treating patients, nor to the Executive Committee until the Data and Safety Monitoring Committee decides to refer these to the Executive Committee. Results of all data analyses will first be presented to the DSMC by the Coordinating Center unless this committee has given other instructions.

The DSMC will be selected by the Directors of the National Eye Institute and National Institute for Child Health and Human Development. It will include two neonatologists and two ophthalmologists who are not affiliated with a participating study center, two statisticians not affiliated with the Coordinating Center or The University of Rochester, a neonatal nurse specialist, an ethicist, and the following ex-officio members: Study Chair,
Study Headquarters Project Director, Director, Co-Director and Protocol Monitor of the Coordinating Center, and a representative from the National Eye Institute, National Institute for Child Health and Human Development, and National Institute of Nursing Research.

The DSMC will review the initial design of the study, including patient recruitment methods and the informed consent procedures and forms, and provide approval before investigational procedures are carried out. The Data and Safety Monitoring Committee will be informed of all changes in the protocol.

The DSMC periodically reviews the study results and evaluates the treatment for beneficial and adverse effects. The Data Monitoring Reports, distributed by the Coordinating Center, will be reviewed only by the DSMC until such time as the data indicates that a change of protocol is required. Recommendations for protocol change will be based on the majority opinion of the DSMC. Each non ex-officio member of the DSMC will have a vote in all decisions. A minority opinion may be prepared at the discretion of the dissenting members of the Committee. The DSMC makes recommendations pertaining to the study to the Director of the NEI. After consideration by the Director of the NEI, these recommendations are referred to the Executive Committee for implementation. The Executive Committee may appeal such decisions by sending a dissenting statement back to the DSMC for reconsideration. The second opinion by the DSMC will be binding.

The Chair of the DSMC will convene a meeting prior to randomization of infants and then at least once per year to review Data Monitoring Reports prepared by the Coordinating Center. Any member of the Committee may request a meeting if they feel data provided within interim reports warrant an additional meeting.

The DSMC will utilize most of the responsibilities outlined in Hawkins (1991) Controlled Clinical Trials 12:424-437, with the following exceptions: The DSMC should not decide that a particular data item be deleted. Their role should be advisory in general, concerned with the overall conduct of the study rather than details. However, they should be strongly involved with treatment effects, quality of the study, patient safety, and early stopping. They should not be involved in the writing process, except insofar as this might affect patient safety or trial quality. They reserve the right to review and comment on papers prior to publication, and national presentations. The DSMC will recommend times and individuals for external review of the Coordinating Center, but not personally conduct the review. Evaluating performance of individual centers should be the responsibility of the Executive Committee, but the Coordinating Center should notify the DSMC of unacceptable performance. The DSMC should not make disciplinary decisions, which are the responsibility of the Executive Committee, unless the Executive Committee fails to meet its responsibilities. This list, given in Exhibits 3-5 and 3-6, summarizes responsibilities the Committee has adopted.
EXHIBIT 3-5
TREATMENT EFFECTS MONITORING

<table>
<thead>
<tr>
<th>Responsibility</th>
<th>1</th>
<th>Y</th>
<th>Y</th>
<th>Y</th>
<th>Y</th>
<th>Y</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>evaluate accumulating data for treatment benefit or harm</td>
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<tr>
<td>recommend data-based protocol changes</td>
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<td>assure study conducted ethically</td>
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<td>suggest data analyses</td>
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<tr>
<td>assess data quality</td>
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<tr>
<td>determine when data may be released</td>
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<td></td>
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<tr>
<td>monitor sample size assumptions</td>
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<tr>
<td>decide when the major study question has been answered</td>
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<tr>
<td>advise writing teams regarding data interpretation</td>
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</tbody>
</table>

1 - Committee will not be involved in writing process, except insofar as this might affect patient safety or trial quality.
### EXHIBIT 3-6

**STUDY OVERSIGHT**

<table>
<thead>
<tr>
<th>Responsibility</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>review/approve study design and methods</td>
<td>Y</td>
</tr>
<tr>
<td>alert/advise study leaders about procedural/ethical issues</td>
<td>Y</td>
</tr>
<tr>
<td>advise NEI regarding study conduct or policy</td>
<td>Y</td>
</tr>
<tr>
<td>review/approve major changes to study protocol</td>
<td>Y</td>
</tr>
<tr>
<td>evaluate performance of individual study centers</td>
<td>Y</td>
</tr>
<tr>
<td>monitor study progress on behalf of the NEI</td>
<td>N</td>
</tr>
<tr>
<td>review/approve manuscripts/presentations using study data</td>
<td>Y</td>
</tr>
<tr>
<td>provide an external review of coordinating center</td>
<td>Y</td>
</tr>
<tr>
<td>decide data items to be deleted</td>
<td>Y</td>
</tr>
<tr>
<td>review/approve ancillary studies</td>
<td>Y</td>
</tr>
<tr>
<td>recommend changes to study organization</td>
<td>Y</td>
</tr>
<tr>
<td>provide external review of other resource centers</td>
<td>Y</td>
</tr>
<tr>
<td>arbitrate disputes regarding data reporting</td>
<td>Y</td>
</tr>
</tbody>
</table>

1. Committee will recommend times and individuals for the external review of the Coordinating Center, but not personally conduct the review.
3.2.7 Training and Certification Faculty

The Training and Certification Faculty will develop a training program and establish certification criteria. This group is composed of ophthalmologists and neonatologists from NEI, NICHD and Alternative Funded Study Centers.

3.2.8 Study Headquarters

The Study Chair and the STOP-ROP Study Headquarters are located at the University of Rochester, and are responsible for the overall supervision of the study. Adequate professional and clerical personnel will be employed to:

A. Maintain contact with the Coordinating Center (EMMES) and the individual Study Centers and to supervise the overall study

B. Organize and conduct training sessions for participating physicians and subsequent progress meetings of the Executive Committee and Technical Group

C. Produce and distribute instructional visual aids for investigators and parents of patients

D. Maintain sufficient records of the progress of the study to enable informed participation in the meetings of the DSMC whenever necessary

E. Maintain surveillance over the world literature on retinopathy of prematurity to permit prompt implementation of new information.

Dr. Dale Phelps, the Principal Investigator for STOP-ROP (also known as the Study Chair), provides ongoing consultation to the Coordinating Center and the DSMC on matters pertaining to any problems in the conduct of the study, especially technical, medical aspects of study procedures. She directs the meetings of the Technical Group and chairs the meetings of the Executive Committee and Editorial Committee. (see Editorial Policies).

3.2.9 Coordinating Center

The Coordinating Center, located at The EMMES Corporation, Potomac, Maryland, is responsible for developing the Manual of Procedures, collecting, monitoring and analyzing study data, ensuring that the provisions of the Manual of Procedures are carried out by all participating units, and coordinating study activities. Coordinating Center staff include professionals in biostatistics, epidemiology, data processing, administration, and communication coordination. Consultants are used to supplement the staff for appropriate specialized tasks.
The staff at the Coordinating Center include the following:

- Director
- Co-Director
- Protocol Monitor
- Administrative Coordinator
- Data Coordinator
- Computer System Group

The Director and Co-Director are in charge of the Coordinating Center and work closely with the Protocol Monitor and Administrative Coordinator, who is responsible for all logistic and administrative support. The Data Coordinator is responsible for maintaining the currency and integrity of the STOP-ROP database, and the Protocol Monitor assists in training and certifying clinic staff and participates in periodic Protocol Review Site Visits [see section 10.3], and Protocol Monitoring Telephone Calls [see Section 10.2]. The Protocol Monitor also serves as a staff specialist for dealing with problems associated with accrual. The Computer System Group is responsible for the design, development, and maintenance of the STOP-ROP data system. The hardware and software components of the STOP-ROP Data System are located at the Coordinating Center.

Coordinating Center staff have major responsibility for developing the statistical design and the operational and analytical methodology, and are also responsible for collecting, editing, analyzing, and storing all data received from the Study Centers. Some of the specific functions of the Coordinating Center staff are to:

A. Collaborate with other study investigators in developing and pretesting study procedures, forms, and the Manual of Procedures

B. Develop a Data Management Handbook for Study Coordinators

C. Reproduce and distribute data collection forms

D. Coordinate communications among the centers

E. Coordinate certification of clinic staff and the Study Centers

F. Assist in training clinic staff in the study procedures

G. Develop a randomization scheme for the clinical trial portion of the study

H. Screen participants for eligibility and randomize to the treatment groups
I. Maintain and distribute pulse oximeters and laptop computers to Study Centers when all study oximeters are in use at the center

J. Review visually and electronically all data transmitted on standardized STOP-ROP forms for completeness, accuracy, and consistency and notify Centers about sources of errors

K. Maintain a current computer master file of edited study data and conduct database assessments targeted at maintaining the integrity of the database, including comparisons of data forms of the Coordinating Center with source documents (e.g., medical record, chart notes) at the Study Center; verify existence of all enrolled infants; monitor adherence of the Study Centers to the protocol; and develop cumulative baseline and endpoint assessments

L. Prepare periodic reports on the performance of the Study Centers including participant accrual and eligibility rates

M. Conduct regularly scheduled, structured Protocol Monitoring telephone calls with the Study Coordinator at each Study Center

N. Prepare an analysis plan in conjunction with the Data and Safety Monitoring Committee [see section 11.6] and periodically analyze the frequency of specified events including adverse reactions, visual function parameters, and other outcomes and report to the Data and Safety Monitoring Committee

O. Prepare recruitment, technical, and statistical reports for meetings

P. In collaboration with Study Center investigators, prepare scientific reports for publication.

One of the routine functions of the Coordinating Center is to meet the many administrative, logistic, and communication requirements of STOP-ROP. To maintain efficient communication among the participating Study Centers, the various STOP-ROP committees, and the NEI, the Coordinating Center maintains a roster of all STOP-ROP personnel. This roster lists the names and addresses of all participating units, the names and telephone numbers of all STOP-ROP staff members, and the names and telephone numbers of current committee members by committee designation. STOP-ROP personnel also are listed alphabetically.

STOP-ROP is supported by a network of committees. For most committee meetings, the Coordinating Center provides logistic support. The Coordinating Center collaborates with STOP-ROP leadership to:

- Determine optimal meeting dates
- Select meeting sites based on cost and convenience
• Reimburse DSMC members for expenses and provide honoraria
• Communicate information about meetings to committee chairmen and meeting participants
• Prepare meeting materials
• Provide logistical support on site
• Duplicate and distribute materials prior to each meeting
• Prepare and distribute minutes of the meetings
• Follow-up on all action items after each meeting
• Coordinate conference calls.

The Coordinating Center supports the preparation, duplication, and dissemination of administrative and technical reports and manuscripts. These documents include:

• Manual of Procedures
• Data Management Handbook
• Participant recruitment materials
• Meeting minutes
• Newsletter
• Statistical reports
• Bibliographies
• Abstracts
• Manuscripts for publication
• Roster of STOP-ROP personnel

Coordinating Center staff work closely with clinicians, statisticians, writing committees, protocol development committees, scientists, and authors. The staff routinely help to:

• Compile and organize materials
• Coordinate reviews and incorporate comments
• Summarize background materials
• Write administrative reports
• Edit technical language to accommodate lay readers
• Ensure that presentations are visually effective.

3.2.10 Study Centers

Each center for patients in the STOP-ROP study is known as a Study Center. Centers will be designated as National Eye Institute Centers, members of the Neonatal Network, or Alternative Funded Centers. Support for such centers is derived from separate grants, or cooperative agreements with the National Eye Institute or through alternative funding sources. These alternative sources must be identified and approved by the National Eye Institute Project Officer prior to initiation of Study Center participation. The function of the Study Center is to carry out the provisions of the Manual of
Procedures at a local level, regardless of funding sources. Equipment support (pulse oximeter monitors, probes, and laptop computers) and support from the Coordinating Center and Study Headquarters will be provided regardless of funding source.

Each Study Center will be headed by a Principal Investigator (PI) who will represent the center at meetings of the Technical Group. The professional and clerical organization of each Study Center will differ in some details.

The PI at each center will designate one person (the Study Center Coordinator) with adequate time commitment to the STOP-ROP study to be responsible for supervising the day-to-day study operations. Some large centers may require more than one Study Center Coordinator to fulfill all the responsibilities of the position (this is dependent upon the number of enrolled study patients and the set-up of the center).

Since the Coordinator will be in extensive contact with the infants' parents, it is important that this individual have the ability to deal well with people. The rapport which frequently develops between a parent and the Coordinator is extremely important during the course of the study to assure their continued cooperation. Parents frequently turn to the Coordinator for clarification or confirmation of their discussions with the physician, and it is therefore extremely important that the Coordinator be a mature and responsible person with a thorough understanding of the protocol, study design, and rationale, as well as retinopathy of prematurity.

The Study Center Coordinator is responsible for such critical matters as appointment scheduling, follow-up procedures, keeping appropriate study records, checking for completeness of forms, transmitting data to the Coordinating Center, and handling communications on data processing with the Coordinating Center, including responding to edit statements. Adequate provision must be made for backup during absences and replacement if necessary. Also, the Study Center Coordinator is responsible for ensuring that all infants with Prethreshold ROP are referred to the study and entered in the Patient Register (STOP 00). The Study Center Coordinator ensures compliance with the STOP-ROP Manual of Procedures and participates in regularly scheduled structured telephone calls with the Protocol Monitor from the Coordinating Center [see Chapter 10].

In addition to the PI (if an ophthalmologist), the presence of a minimum of one other certified ophthalmologist is required for the conduct of the study, but for practical purposes, at least three ophthalmologists are preferred to provide adequate coverage. The ophthalmic investigators will be subspecialty trained in pediatric or retinal diseases or have had special training/experience with ROP. At least one of each subspecialty should be represented in the group. These ophthalmologists must undergo training in the techniques used in the examinations and treatment within this study.

Each Study Center will have at least one designated neonatologist investigator at each participating hospital who will supervise medical management of study patients and
who will be committed to ensuring referral of all eligible infants to this study. The neonatologist will be responsible for organizing in-services for nursery personnel to maximize cooperation among the pediatric and ophthalmologic staffs for the conduct of this study in the nursery. A second neonatologist is strongly recommended.

3.2.10.1 Alternative Funded Centers

Alternative Funded Centers derive their support from alternative sources which are identified and approved by the National Eye Institute Project Officer prior to initiation of Study Center participation. Approval of Alternative Funded Centers is based upon ability to execute the STOP-ROP protocol. In addition, financial support for investigators, travel allowance, and support space must be provided by the Alternative Funded Center. The procedure for application as an Alternative Funded Center is outlined in Appendix C. Equipment and clerical/data support for Alternative Funded Centers is addressed in Section 3.2.9.
CHAPTER 4

STUDY POLICIES
CHAPTER 4

STUDY POLICIES

4.1 ADHERENCE TO MANUAL OF PROCEDURES

All members of the STOP-ROP Study Centers participate in the development, review, and acceptance of this Manual of Procedures. The manual is formally approved by the STOP-ROP Operations Committee, STOP-ROP Executive Committee, and the Data and Safety Monitoring Committee (DSMC). It is essential to the success of the study that all STOP-ROP investigators adhere to the procedures outlined herein. If any STOP-ROP investigators find that, for whatever reason, adherence to these procedures is difficult or not possible, they should discuss the problem with the Study Chair or the Protocol Monitor.

4.2 INFORMED CONSENT AND LOCAL IRBs

The Strong Memorial Hospital, University of Rochester School of Medicine is served by an Institutional Review Board (IRB) under the National Institutes of Health General Assurance #M1357. This Board is composed of the appropriate designated individuals and reviews all projects to be performed with human subjects prior to their initiation. Each project is required to provide an annual report for review and re-approval in order to continue. In addition, any unanticipated side effects must be reported immediately to the Board. All Study Centers should adhere to the Strong Memorial Hospital requirements of IRBs.

Informed consent shall be obtained from each STOP-ROP parent or designated legal guardian as part of the enrollment process. If the designated legal guardian changes while the infant is participating in STOP-ROP, a new informed consent must be obtained from the current legal guardian [for simplicity, the word parent will be used from this point on. Parent implies either parent or legal guardian]. The Study Center must ensure that parents are adequately oriented to the objectives and procedures of STOP-ROP. To identify potential participants, the Study Center Coordinator (SCC) will attend weekly ophthalmological examinations and notify the Principal Investigator (PI) of potential participants. The PI and SCC will communicate with the parents to assure they are aware that potentially serious ROP is present and that their infant will be monitored for possible participation in STOP-ROP. At this time, parents of potential participants will be provided with the STOP-ROP information leaflet to read. If the infant progresses to Prethreshold ROP and the PI is satisfied that the parents understand the potential risks and benefits of participation in the STOP-ROP protocol, written informed consent will be obtained.

Informed consent is also needed for any additional research procedures that may be part of an ancillary study and may expose the participant to risk or discomfort.
The signed informed consent forms are placed in the participant's file at the Study Center. The Participant STOP-ROP information leaflet and sample informed consent statements to be used are provided in Appendix D and E.

4.3 PROTECTION OF HUMAN SUBJECTS

Prior to enrolling participants each Study Center must submit to the Coordinating Center written approval by the local Institutional Review Board (IRB) and copies of the Study Center local IRB approved informed consent statements. In addition, annual IRB approval letters must also be submitted to the Coordinating Center, in a timely manner. These documents will be forwarded to Study Headquarters.

4.4 INTENTION TO TREAT

STOP-ROP will utilize an intention to treat policy for all primary analyses. From a statistical point of view, any other course of action involves special treatment of a non-randomly selected subset of patients. Assume, for example, that there is actually no treatment effect. Randomization will then cause both arms to have the same mix of favorable and adverse outcomes. But suppose the physician has identified a supplemental-oxygen patient whose outcome is likely to be adverse. For example consider an infant randomized to supplemental oxygen, but the physician is unwilling to raise the oxygen enough to meet the supplemental oxygen treatment range, or the infant is too medically unstable to meet the supplemental range. The attending physician’s oxygen order results in the infant’s saturation levels within the conventional range. If, in our analysis, we transferred all such patients to the conventional oxygen arm, or even just dropped them from the analysis, it would seem as if conventional oxygen had a detrimental effect. Therefore, while we are unable to raise the oxygen and must manage this infant using the conventional oxygen treatment, we will analyze him or her statistically as a member of the supplemental oxygen group.

From an operational point of view, we analyze not the treatment itself, but rather a treatment policy. Neither in the trial under consideration, nor in future clinical practice, can we force humans into a Procrustean treatment schedule. Our primary concern is thus treatment policy, not outcome when treatment is possible. The latter is an interesting secondary research topic.

It is not always obvious when to invoke the intention-to-treat policy. Consider one reviewer’s comments:

"... a patient is randomized to the conventional oxygen administration group with pulse oximeter saturations from 89% to 94%, but after two to three weeks the lung disease improves enough that the patient is no longer able to reach these lower pulse oximeter saturation levels. How will these patients be analyzed?"
For STOP-ROP, once a patient is randomized to a particular group, he/she should always be part of that group for primary analyses. Therefore, we will consider the patient to be in the conventional oxygen group. Thus, while a patient's primary analysis group is determined strictly by randomization, clinical considerations may cause his or her actual management group to change. Secondary analyses will explore dose-response relationships utilizing actual saturation levels during treatment.

4.5 MASKING

Clinical trials attempt to minimize bias on the part of study examiners through a mechanism known as masking. In STOP-ROP, the neonatologists, parents, NICU nurses, and Study Center Coordinators (SCC) at individual Study Centers will know the participant's oxygen treatment group, however the examining certified ophthalmologists will not know and thus will be masked as to the oxygen treatment group. Therefore, at best STOP-ROP can be a single-masked study. Single masking of this study will be maintained for the duration of follow-up by examining ophthalmologists. To facilitate this objective, SCCs will be required to close the laptop monitor during the infant's eye examination. Instructions regarding the need to maintain masking of the examining ophthalmologist will be communicated to parents, nurses, and physicians, prior to each examination.

Every effort should be made to have retinal examinations performed by a masked examiner.

4.6 PUBLICITY

The Executive Committee should be informed of local publicity efforts to enroll study infants. Personnel at each Study Center should refer requests from news media for information about STOP-ROP to the Information Office of the National Eye Institute. All publicity and press releases for STOP-ROP study results must be approved by the Executive Committee.

At certain times, it may be appropriate for the Principal Investigator of the Study Center to respond to requests from the media in his/her local community. Information given by the PI should emphasize the following:

- STOP-ROP is a collaborative, multicenter study.
- The local center is only one of many.
- The study is funded by the National Eye Institute, with additional support from the National Institute for Child Health and Human Development and the National Institute of Nursing Research (some centers may also have alternative funding sources).
• Results of the clinical trial will not become available until meaningful findings emerge, as determined by the Executive Committee after review of the recommendations of the Data and Safety Monitoring Committee.

No statements concerning study data may be made without the approval of the Director of the National Eye Institute (NEI), Data and Safety Monitoring Committee and Executive Committees. Inquiries for additional information not already in the public domain should be referred to the Study Chair.

4.7 DISCLOSURE OF STUDY RESULTS

Knowledge of interim results of the clinical trial could compromise the efforts by Study Centers to enroll and maintain follow up of study infants. For this reason, reports of such results are submitted by the Coordinating Center only to the Data and Safety Monitoring Committee (DSMC) which is responsible for monitoring the results for safety and efficacy. The DSMC will then submit these results to the Director of the NEI. After consideration by the Director of the NEI, these recommendations are referred to the Executive Committee for implementation.

The results of the trial will be made available to participating investigators at a time specified by the DSMC as soon as beneficial or harmful effects are established or the trial has concluded. Investigators should refrain from attempting to determine the overall results of the study from their own Study Center experience.

Disclosure of STOP-ROP results, at appropriate times, to investigators, participants, the scientific community, and the public will be coordinated closely by the Information Office of the National Eye Institute, the Executive Committee, and the STOP-ROP Coordinating Center. Prior to disclosure of study results, the following steps should be considered:

• Notify Principal Investigators at participating centers

• Prepare data, analysis, and manuscript for peer review

• Obtain peer review through an appropriate journal, seeking expedited review from the chief editor if appropriate

• Provide a mechanism for physicians to obtain additional information and support for patients during the interval between acceptance for publication and actual release

• Prepare material for utilization by the media

• Coordinate press releases with the publishing journals
Facilitate distribution of reprints

4.8 SCIENTIFIC PUBLICATIONS AND PRESENTATIONS

4.8.1 Generation of Publications and Presentations

The Executive Committee will develop procedures for generating scientific publications and presentations emanating from the design and data collection of the STOP-ROP study. This committee will serve as the Editorial Committee and will make recommendations for the appointment of writing teams composed of Study Center participants. Writing teams shall be responsible for developing final and mainstream reports on a voluntary rotating basis.

Final reports are concerned with data which tests the specific aims of the STOP-ROP study. Mainstream reports concern the entire database results collected by the STOP-ROP Study Group but not the specific aims of the study. Additional categories of manuscripts will be "Ancillary" and "Parallel" studies and are described in 4.8. Prior to publication, copies of STOP-ROP reports are sent to all members of the Executive Committee for information and comment. Following Executive Committee review, the manuscript will be distributed to the Data and Safety Monitoring Committee for their information prior to publication. Reprints of published reports are mailed to each Study Center for distribution to staff. Five Reprints of each report are sent to the Coordinating Center for the STOP-ROP library.

4.8.2 Editorial Review

Abstracts of papers to be presented at scientific meetings and manuscripts to be submitted for publication that deal with the design of STOP-ROP or are based on STOP-ROP data, whether they pertain to a single STOP-ROP center, several STOP-ROP centers, or all STOP-ROP centers must be approved by the Executive Committee prior to publication or presentation. Reports on ancillary and parallel studies, as well as oral presentations which address the STOP-ROP study or study results must be similarly approved. The only exception is oral presentations to local groups on the design of STOP-ROP, which do not need to be approved by the Executive Committee.

Leaders of writing teams, in submitting a STOP-ROP report for publication, should include a copy of the approved letter from the Chair of the Executive Committee.

4.8.3 Authorship

Final STOP-ROP Reports will be numbered serially and authored by the "STOP-ROP Cooperative Group". For example:

Title: Incidence of Threshold ROP in Premature Infants Receiving Supplemental Oxygen. STOP-ROP Report No.2
Author: STOP-ROP Cooperative Group

Final STOP-ROP Reports will be published by the STOP-ROP Cooperative Group but written by a Writing Committee established by the Executive Committee. Participants of the STOP-ROP Study Group who have the approval of their Principal Investigators and have served for at least two years in a major role within the study will be listed at the conclusion of each report and be considered as author or contributor. All study personnel who are proposed by their PI will be listed in monographs at the conclusion of the report.

Mainstream STOP-ROP Reports will also be numbered, but they will be authored by the members of the writing team and the STOP-ROP Cooperative Group. For example:

Title: ROP Regression with supplemental oxygen therapy.
STOP-ROP Report No. 7

Authors: Ford, GP, James, KI, and STOP-ROP Cooperative Group

Mainstream STOP-ROP Reports will be authored by the writing group who formulates the research question, conducts data analysis and writes the report. Participants of the STOP-ROP Study Group who have the approval of their PI and have served for at least two years with the study will be listed at the conclusion of the report and be considered as author or contributor. All study personnel who are proposed by their PI will be listed in monographs at the conclusion of the report.

4.8.4 Acknowledgements

Final and Mainstream STOP-ROP Reports will acknowledge support of the study by grants from the National Eye Institute, National Institutes of Health, Department of Health and Human Services (1U10 EY09962), and additional support from the National Institute of Child Health and Human Development, and the National Institute of Nursing Research.

4.9 ANCILLARY AND PARALLEL STUDIES

Ancillary and parallel studies are investigations that are conducted concurrently with STOP-ROP and involve STOP-ROP participants. Ancillary studies are STOP-ROP studies; they involve participation by the STOP-ROP Executive Committee and the Coordinating Center. Parallel studies are not STOP-ROP studies; they do not involve participation by the STOP-ROP Executive Committee or the Coordinating Center.
4.9.1 Definitions

4.9.1.1 Ancillary studies. An ancillary study meets the following criteria:

(1) The research is conducted by STOP-ROP investigators on STOP-ROP participants.

(2) The goals of the study are consistent with STOP-ROP objectives.

(3) The research requires supplementary clinical observations or procedures on STOP-ROP participants.

(4) The STOP-ROP Executive Committee, with NEI approval, has designated the study as a STOP-ROP ancillary study, thus endorsing participation by (1) the STOP-ROP Operations Committee, (2) Study Headquarters, and (3) the Coordinating Center in study development, conduct, data processing, and data analysis.

(5) Consent forms for ancillary studies are approved by the local IRB and obtained from parents in a manner separate from the STOP-ROP study.

Ancillary studies by individual STOP-ROP investigators or groups of STOP-ROP investigators are encouraged because they can enhance the value of STOP-ROP and increase the motivation and interest of investigators in STOP-ROP. However, to protect the scientific integrity of STOP-ROP and to prevent a drain on STOP-ROP resources, all proposals for ancillary studies, whether or not they involve the need for supplemental funds, must be submitted for approval to the Executive Committee.

4.9.1.2 Parallel studies. A parallel study meets the following criteria:

(1) The research is conducted on STOP-ROP participants but does not need to be carried out by STOP-ROP investigators or involve STOP-ROP. The research may have started before or after the inception of STOP-ROP.

(2) The STOP-ROP Operations Committee, Study Headquarters, and the Coordinating Center are not participating in the study.

4.9.2 Approval of Ancillary and Parallel Studies

4.9.2.1 Studies conducted by STOP-ROP investigators. An ancillary study conducted by STOP-ROP investigators must be approved by the Executive Committee and the NEI at the time of Study Center application for STOP-ROP. Applications after the initiation of the STOP-ROP protocol must be submitted to the Executive Committee for approval. Approval by the NEI and the Executive Committee is contingent on local IRB approval.
A copy of the local IRB approval must be sent to the Coordinating Center for forwarding to Study Headquarters, as well as subsequent approvals of modifications. Approval of ancillary studies is required to ensure that studies will not:

- adversely affect participant enrollment or cooperation
- jeopardize the public reputation of STOP-ROP
- result in premature release of STOP-ROP outcome data
- complicate the interpretation of STOP-ROP results
- substantially divert study resources at one or more Study Centers, Study Headquarters, or the Coordinating Center.

Additionally, approval by the NEI and Executive Committee of ancillary studies is needed to assure:

- the study's scientific merit
- the risks to participants do not outweigh potential benefits
- the participant's rights are not violated.

Approval is not needed for parallel studies because they are not STOP-ROP studies: they do not involve participation by STOP-ROP resource centers. The review of parallel studies by STOP-ROP is limited to indicating that the studies are not expected to jeopardize the scientific merit of STOP-ROP. Because STOP-ROP has no investigative role in parallel studies, STOP-ROP has no responsibility for their scientific merit or ethical conduct. Such reviews are conducted by discussion at site visits and at other times as needed by phone and letter.

STOP-ROP investigators who wish to conduct an ancillary study should submit a proposal to the Chair of the STOP-ROP Study. The Chair will distribute it to all members of the Executive Committee. After review of the proposal for completeness and clarity, the Chair will summarize the committee's comments and forward these comments to the applicant for an opportunity to amplify, clarify, or withdraw the proposal. Members of the Executive Committee will then review the amended proposal for approval. The Chair will then prepare a consensus statement of the Executive Committee, and indicate any final reservations or objections to the proposal and forward this to the investigator requesting approval for the ancillary study.

Proposals submitted for approval should:

- Briefly describe in narrative form the objectives, methods and significance of the study and provide full details on procedures (eg, examinations, tests, drawing of blood, additional questionnaires, psychiatric testing) to be carried
out on participants or their parents. If intended as an ancillary study, the
detail should be sufficient to evaluate the study's scientific merit.

- State the number of STOP-ROP and non-STOP-ROP participants to be
  enrolled.

- State the amount of time by which STOP-ROP participant hospitalization
time will be prolonged.

- State the number of STOP-ROP and non STOP-ROP additional examinations
to be required for STOP-ROP participants and their length of time.

- State whether participants will sign an informed consent and, if so, include
  a copy of the form.

4.9.2.2 Parallel studies not conducted by STOP-ROP investigators. For a parallel
study that is not conducted by STOP-ROP investigators, STOP-ROP has no role in
approving the study; however, STOP-ROP can play a role in preventing STOP-ROP
participants from taking part in parallel studies that are demanding on the participants
time.

As part of the eligibility evaluation, a potential STOP-ROP infant’s parents will be
asked about their participation in other studies. Infants participating in other studies
should not be enrolled in STOP-ROP unless the PI is assured that this participation will
not interfere with their successful participation in STOP-ROP. Although the PI has no
direct control over parallel studies conducted by non-STOP-ROP investigators, if the PI
becomes aware of a parallel study started after inception of STOP-ROP that may interfere
with STOP-ROP, the PI should bring this problem to the attention of the Executive
Committee through the Chair.

4.9.3 Funding and Publication of Ancillary and Parallel Studies

4.9.3.1 Funding. NEI STOP-ROP grant funds may not be used to support the
conduct of ancillary or parallel studies. For additional funds, the investigator may wish
to submit an National Institute of Health R01 grant application or apply to another funding
agency. If no additional funds are required, the investigator may proceed with an ancillary
study as soon as it is approved by the NEI and Executive Committee.

4.9.3.2 Publication. Abstracts and manuscripts of ancillary studies. Abstracts and manuscripts of ancillary
studies that are intended to be presented at scientific meetings or submitted for scientific
publication must be reviewed and approved by the STOP-ROP Executive Committee
(Section 4.6). The STOP-ROP Executive Committee will review these abstracts and
manuscripts to assure that they do not compromise the conduct of STOP-ROP or the
interpretation of STOP-ROP results.
Abstracts and manuscripts of parallel studies. Because these abstracts and manuscripts are beyond the direct control of STOP-ROP, there is no official review role for STOP-ROP. Nevertheless, STOP-ROP investigators or their colleagues who are conducting these studies should avoid referring to STOP-ROP in their publication and presentations.

4.10 DISPOSITION OF INFANTS AT STUDY CONCLUSION

4.10.1 Infants Enrolled in the Study, Oxygen Treatment Finished

The parents of study infants will be notified by letter of study completion, and provided with a summary of STOP-ROP results. Efforts will be made to coordinate parent notification with scientific publication, particularly if there is an associated press release.

4.10.2 Infants Enrolled in the Study, Oxygen Treatment Current

It is unlikely that infants will be receiving oxygen treatment at the conclusion of the study. The exception to this will be early termination of the study by the DSMC. When this occurs, infants randomized to the preferred oxygen treatment arm will continue their oxygen treatment; those infants receiving the less preferred oxygen treatment will be changed to the preferred oxygen treatment arm.

4.10.3 Infants Not Enrolled

Potential study infants at Study Centers who have not been enrolled will be managed by the plan described in Section 5.4, which addresses the management of Human Subjects at the conclusion of the study.
4.11 ADVERSE EXPERIENCE AND DEATH REPORTING

4.11.1 Definition of Adverse Experience

An adverse experience is defined as any toxicity, reaction, event, or effect which may be associated with participation in the STOP-ROP study. The goal of adverse experience reporting is to discover whether assigned oxygen treatment has adverse consequences. The STOP-ROP protocol requires reporting of any death or life-threatening event to the Data and Safety Monitoring Committee. The list below enumerates other adverse experiences that require reporting. The last list item stipulates reporting of other serious unexpected event or events believed to be treatment-related. Statistical analysis of this last element will be problematic.

Adverse experiences:
- Excessive apnea and bradycardia (number of episodes is triple the baseline)
- Documented hyperoxia (paO₂ > 120 torr) while in the target range
- Documented hypoxia (paO₂ < 45 torr) while in the target range
- Seizures
- Necrotizing enterocolitis
- Pneumonia/sepsis with positive culture or requiring antibiotic treatment for more than five days
- Other serious event(s) believed to be treatment-related (specify).

Events that are not adverse experiences:
- Urinary tract infection
- Localized infection
- Gastrointestinal disorders other than necrotizing enterocolitis
- Dermatological disorders.

Rationale: an obvious strategy for adverse experience monitoring is to require the physician to report all events that might be related to treatment. The decision to report must be largely independent of the physician's opinion, otherwise, adverse experiences would seldom be reported in the conventional arm; these events appear to be unrelated to treatment, because the patient is not receiving the treatment. Such underreporting would cause serious bias.

The bias can be avoided by specifying a list of events that require reporting. Unfortunately, no list is complete. But life-threatening and unexpected serious events must be quickly reported; missed events could threaten patient safety.

Objective reporting requires a list, yet patient safety requires more. The only solution is an open-ended list; the last item includes all previously unlisted events that are either serious or suspected by the physician to be treatment-related. Statistical analysis of the last item will be problematic, yet the need for the last item is inescapable.
4.11.2 Reporting Requirements

Study Centers should report adverse experiences and all deaths after enrollment to the Coordinating Center as described below. Deaths are reported even if they are clearly unrelated to the study.

### Reporting Requirements

#### Deaths and life threatening events

Telephone: 1-301-299-8655 and fax: 1-301-299-3991 Death (STOP 12) and/or Adverse Experience (STOP 08) form within 24 hours. Mail STOP 08 and STOP 12 form(s) original(s) within 3 days. If death occurs, mail copy of discharge summary (with name obscured) when available.

#### All other adverse experiences

Mail original Adverse Experience STOP 08 form within 1 week of event.

1. **All deaths and life-threatening events** must be reported to the Coordinating Center within 24 hours of Study Center Coordinator notification. Life threatening events are not intended to include the usual and expected severity of apnea and bradycardic episodes.

2. Report adverse experiences and deaths according to the reporting requirements above, irrespective of whether or not a change in oxygen administration or treatment discontinuation was necessary.

3. If new information is obtained or it is learned that previously provided information was incorrect, mail or fax the corrected material.

Deaths and life-threatening adverse experiences will be reported to the Adverse Experience Monitor of the DSMC by the Coordinating Center. The Coordinating Center will report within 24 hours of notification by a Study Center. These reports will include the treatment course of each infant and will be preceded by warning telephone calls. A summary of all adverse experiences will be provided to the DSMC every six months.
CHAPTER 5

HUMAN SUBJECTS CONSIDERATIONS
CHAPTER 5

HUMAN SUBJECTS CONSIDERATIONS

The safe conduct of a study and the protection of human subjects is a primary guiding principle for all clinical trials. Many aspects of a study are involved with this overriding principle, and these are summarized in this chapter.

5.1 DATA AND SAFETY MONITORING COMMITTEE (DSMC)

The DSMC is charged with the overview of the study design and monitoring of the developing results and potential hazards. These responsibilities and the composition of the committee are more widely described and discussed in Chapter 3. Results of reviews will not be available to the participating ophthalmologists and neonatologists who are treating infants until the National Eye Institute, upon recommendation from the Data and Safety Monitoring Committee, decides to release the results, or until the completion of the study. Results of all data analyses will first be presented to the Data and Safety Monitoring Committee unless this committee has given other instructions.

5.2 PATIENT CARE IMPLICATIONS

5.2.1 Potential Prolonged Hospitalization

Prethreshold ROP indicates that an infant is still at risk for serious sequelae of ROP and should be given oxygen only under controlled conditions with regular monitoring. It has generally not been possible at home, and therefore such infants are often kept in the hospital while still on oxygen to permit the controlled administration of their oxygen. However, if the infant is already at home or close to discharge, the monitoring system (laptop computer and oximeter) may be used at home or in the hospital. Because of this, hospitalization need not be continued if the infant is otherwise ready to be discharged home. The parents can be taught to use the equipment at home.

Insurance companies would be expected to cover the costs of home oxygen administration, but the Study Center would provide the pulse oximeter and laptop computer.

5.2.2 Administration of O₂ to Infants Already on Room Air

Infants with Prethreshold ROP are not eligible for the study unless their state of oxygenation is marginal. Therefore infants with no significant lung disease and pulse
oximetry greater than 94% in room air more than 50% of the time are ineligible. When infants have a pulse oximetry of 89-94% in room air, it is likely that they are normally going to be on and off oxygen as it is weaned from their care and therefore they will be eligible.

5.2.3 Home Oximetry and Oxygen

Monitoring and administration of oxygen can be conducted at home as well as in the hospital. The Study Center Coordinator and hospital nurses will be responsible for teaching the parents the appropriate use of the oximeter, its recording device, and oxygen equipment (Section 7.3.2.4). The infant may be disconnected from the pulse oximeter and computer to be transported to and from the hospital for study exams.

5.3 NIH CONSIDERATIONS

5.3.1 Involvement of Human Subjects

Premature infants at risk for serious ROP almost always weigh less than 1500 grams at birth. The parents of only those infants who are detected as having significant ROP through routine ophthalmic examinations, irrespective of birth weight and/or gestational age, will be approached for informed consent. The intervention causes no immediate medical risk, but the unknown potential long-term problems are real and discussed below in Section 5.3.4.

5.3.2 Source of Research Information

Data will be collected from the existing medical records, and periodic indirect ophthalmoscopy will be performed both for study and patient care purposes. No sensitive data will be collected.

5.3.3 Recruitment and Consent Procedures

All premature infants at risk for ROP are normally examined by a specially trained ophthalmologist no later than 5-6 weeks after birth (Appendix F). The Study Center Coordinators will attend routine screening examinations to ascertain the names of potentially eligible infants. With the permission of the neonatologist and ophthalmologist responsible for the infant's care, the parents of potentially eligible infants will be approached to explain ROP and the study. Written informed consent will be requested after the parent(s) fully understand the study process. An approved Consent Form for the study is provided in Appendix E for use as a prototype.
5.3.4. **Potential Risks**

The infants enrolled in this study are at significant risk (33%) for progressive ROP. The potential benefit of the proposed treatment is that it may reduce the risk of progression. On the other hand, if the hypothesis is incorrect, the oxygen may cause an increased risk of progression of the ROP to more severe stages. In addition to this medical risk, there also exists the potential for prolonged hospitalization and increased cost of hospitalization in some study infants due to altered criteria for discontinuing oxygen.

5.3.5. **Procedures to Minimize Risks**

The study is designed to be more sensitive to stopping for adverse effects and more stringent for demonstration of benefit. Interim analyses will be performed to stop the study early, if indicated (Chapter 11, Section 11.6).

The financial risk to society is believed to be justified by the potential gain in knowledge for preventing vision loss. The potential emotional concerns of prolonged hospitalization can only be handled through discussion and understanding. It is possible to monitor study infants at home with a pulse oximeter and laptop, provided that the parents can understand and demonstrate proper use of study equipment.

5.3.6. **Justification of Risks**

The risk that carefully controlled increased oxygen therapy may worsen the ROP is considered justified because animal data, case control data, and uncontrolled treatment reports suggest that the oxygen therapy may improve ROP. If the hypothesis of this study is proved correct, the savings in vision and total medical costs could be substantial (see cost effectiveness projections in Section 1.5). The number of infants exposed to the risk will be minimized according to the methods described in Section 5.3.5 and in Chapter 11, Statistical Considerations.

5.3.7. **Minorities and Women**

Because infants are enrolled on the basis of their disease process, gender and race are not considerations in selection of eligible infants. Female infants are included, as are infants of all races according to the disease that they develop. The population characteristics should closely match those of the entire population of premature infants with one important difference. Although the population of premature infants has 50% female, 51% caucasian, 39% black and 10% of other races, black infants develop serious ROP far less often and therefore will not be present in the enrolled population at the rate of 39%. Based on the Natural History data from CRYO-ROP on 4,099 infants, we expect the enrolled infants to be 60% Caucasian, 28% Black, 11% other races, and 50% female [see Exhibit 11-1].
5.4 MANAGEMENT OF INFANTS AT THE CONCLUSION OF ENROLLMENT

In the event of early termination for a beneficial effect:

If the study is terminated early because of a clearly significant benefit, all Study Centers will be notified via a telephone call within one week. Pending the detailed examination of the final database and subgroup analyses, parents of potentially eligible infants may be informed of the study and advised that an open label treatment phase is being conducted during the analysis, review, and publication phase of the trial. During the open label phase, all infants will be assigned to the beneficial treatment group.

The IRB at each participating institution is to be informed of these changes. The consent form may need to be updated.

In the event of early termination for an adverse effect:

If there is indication for early termination of the trial because of a significant adverse effect, all enrollment will cease, and each center will be contacted by phone within 3 days to communicate that a "hold" is in progress. Each IRB is to be notified of the "hold" and additional further actions to be taken.

According to the severity of the adverse reactions noted, additional data will be collected on those infants enrolled in the study; subgroup and detailed analyses will be performed to determine the incidence of adverse events. If particular subgroups have been affected, the investigators will be informed immediately. Following the recommendations of the DSMC, the Executive Committee will convene a meeting and mandate appropriate action to ensure human subject protection.

In the event of ended enrollment for predetermined sample size:

If the predetermined sample size has been reached and study enrollment stopped without indication based on interim results, no further infants will be randomized. Pending the results of the data collection and analyses, infants will be treated according to conventional therapy as prescribed by their own physicians.

Regardless of the reason for termination of the study, the results of the STOP-ROP study will be published.
CHAPTER 6

INFANT SELECTION, ENROLLMENT PROCESS, AND STUDY VISIT OVERVIEW
CHAPTER 6

INFANT SELECTION, ENROLLMENT PROCESS AND STUDY VISIT OVERVIEW

Potential study infants should ideally be identified at least a week before they qualify for the study so that their parents will have time to become familiar with ROP and the STOP-ROP study. The target time for randomization is within 24 hours from the initial examination identifying Prethreshold ROP. This chapter describes this process as well as the specific entry criteria, enrollment process, randomization steps and an overview of follow-up visit requirements. Exhibits 6-1 and 6-2 provide flow charts detailing the sequence of events and data requirements before and after randomization.

6.1 IDENTIFICATION OF POTENTIAL SUBJECTS

ROP generally affects both eyes of the infant. An infant who develops Prethreshold disease in one eye or both eyes will be eligible for treatment intervention, which, because it is systemic, will affect both eyes. The Study Center Coordinator (SCC) in each nursery will attend all screening eye examinations to identify and register those infants with progressing ROP. Although criteria for scheduling of initial and follow-up eye examinations may differ among institutions, approval for such criteria must be obtained from Study Headquarters prior to certification of the Study Center. [See recommended ophthalmic examination criteria and follow-up schedule: Section 8.2]

The SCC should closely monitor the examinations performed and be aware of potential study infants before their ROP actually reaches Prethreshold level.

Ophthalmologic exams should be conducted according to the procedures outlined in Chapter 8. Whenever vessels stop in zone 1, or when stage 2 ROP is present in zone 2, the degree of ROP is of enough concern that the parents should begin to receive information about ROP and the study in anticipation of possible progression to Prethreshold ROP. By informing parents at the time this potentially serious ROP is discovered, it may be possible to obtain a signed informed consent on the same day that the infant is diagnosed as having Prethreshold ROP, should that occur. The planned progression of events would be:

a. Examination: Significant ROP present, but less than Prethreshold. The SCC, ophthalmologist, or PI will inform the attending neonatologist of the significant ROP and seek permission to contact the family. An introduction from the neonatologist is recommended.
EXHIBIT 6-1
SAMPLE SUMMARY DETAILED FLOW CHART

Infant has significant ROP

Parents contacted, study explained

Infant develops prethreshold and is entered on Patient Register

Consent signed

Prethreshold confirmed by a certified examiner

Patient enrolled

RANDOMIZE

Conventional oxygen
Oximetry = 89 - 94 %

MINIMUM
2 weeks Rx

Supplemental oxygen
Oximetry = 96 - 99 %

Retinal examination and neonatal assessment weekly

Eye progresses to Threshold ROP or beyond, confirmed

Ophthalmic endpoint:
Adverse outcome, infant becomes eligible for other treatment

Regression begins

Vessels progress to ora serrata, OR zone 3 for 2 consecutive weeks

3-Month post term due date ophthalmic and neonatal outcome examination
# EXHIBIT 6-2

## DATA COLLECTION FLOW SHEET

<table>
<thead>
<tr>
<th>STOP-ROP FORM</th>
<th>STOP 00</th>
<th>STOP 01</th>
<th>Randomization Log STOP 02</th>
<th>STOP 03</th>
<th>STOP 10</th>
<th>STOP 10A</th>
<th>STOP 11</th>
<th>STOP 04</th>
<th>STOP 05</th>
<th>STOP 06</th>
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<tr>
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<td>Pre-Randomization; Patient Registry</td>
<td>Pre-Randomization; Baseline Eligibility</td>
<td>Post Randomization (at 8, 16, and 24 hours)</td>
<td>Baseline and as needed</td>
<td>Weekly</td>
<td>At time of Initial Discharge</td>
<td>At time of Initial Discharge or 3-month exam</td>
<td>At time of Rehospitalization</td>
<td>3 Months (10-14 weeks post due date)</td>
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*Other forms to be completed as needed:*
- Protocol Anomaly (STOP 06)
- Transfer (STOP 07)
- Adverse Experience (STOP 08)
- Death (STOP 12)
b. Parent(s) will be specifically informed of the nature of their infant’s ROP and given an information leaflet which describes ROP and the study.

c. A copy of the Informed Consent form will be provided to the family. The family will be told that if their infant’s ROP progresses to Prethreshold in either eye, they will be asked to give permission for the infant to be randomized and treated within 24 hours.

d. The date and time of the next examination will be given to the family, with plans made for the means of communication following that examination. If the family will not be available at the time of the next scheduled examination (live far from the hospital, out of town, etc), investigators should request that parents sign a consent form in anticipation of the examination, with the understanding that the study would not be started unless the ROP actually progressed, and that the investigators would make all possible efforts to reach the family by phone about the examination results before actually randomizing the infant to either study group.

When the disease reaches Prethreshold level, the following information will be recorded in a Patient Register (STOP 00): Name, hospital number, date of birth, birth weight, gender, race, gestational age (31), date of exam, summary of the ophthalmic examination findings, pulse oximetry and oxygen source. Gestational age is determined by early dating ultrasound (less than 15 weeks) or, when it is unavailable, by the admitting neonatologist. When there is a discrepancy greater than 3 weeks between the early dating ultrasound and other estimates, the STOP-ROP neonatologist must adjudicate. Following the remaining steps described in this chapter, the final column in the register is completed. This column notes whether the infant was enrolled in the trial, and if not, the reason for exclusion. The information in the register will be mailed to the Coordinating Center monthly.

Through the processes above, the SCC will be aware of all infants who have zone 1 or zone 2 vessels prior to their discharge home. If such an infant is to go home, or to be transferred to another special care nursery, yet has still not shown signs of regression with vessel growth into zone 3 or progressed to Prethreshold ROP, the SCC must assure a line of communication and contact with the family and the physicians who will be following the infant’s ROP status. The SCC can be extremely helpful to the physicians and family in this regard, and at the same time maintain the needed contact to identify and enroll potential subjects in a timely fashion.

6.1.1 Eligibility Criteria

To meet entry criteria for STOP-ROP, an infant must be judged by two examiners, one of whom must be a certified study ophthalmologist, to have Prethreshold ROP in one or both eyes. The confirming examination by a study certified ophthalmologist should be scheduled within 24 hours of the first exam. The goal is to perform randomization within 24 hours from the first examination identifying Prethreshold ROP (see section 6.6 on Late
Entry if more than 24 hours. To facilitate this objective, Study Center screening examinations should be performed on Monday, Tuesday or Wednesday, in order to schedule confirming examinations within 24 hours.

Prethreshold ROP is defined as:

**Zone 1: any ROP.** Vessels which stop in zone 1 without a demarcation line (i.e. zone 1 immature) are not considered Prethreshold, but once stage 1 or 2 ROP of any number of clock hours can be identified in zone 1 without plus disease, the infant (eye) has Prethreshold disease. If stage 3 develops or if plus disease develops in the presence of any stage ROP in zone 1, then that eye is to be considered at Threshold, and is beyond entry criteria for this study. An eye with dilated or tortuous vessels with no stage of ROP is not considered to have ROP of any severity.

**Zone 2: Stage 3.** If an infant has any number of clock hours of stage 3 disease in zone 2, that eye is at least at Prethreshold. The following procedure should be used to determine the number of clock hours of stage 3 disease and whether a run of disease is contiguous. If the run has gaps (contains segments of ROP that are less than stage 3), this may alter the number of hours in the run, and also change a continuous run to a discontinuous run. The decision is made as follows: if a single gap is less than 1/2 clock hour, it may be ignored. If there is more than one gap, the examiner must estimate the total sum of all gaps within the run of ROP. If the sum is equal to or greater than 1/2 hour, it must be deducted from the run, and the run must be considered as discontinuous. If the sum is less than 1/2 hour, it can be ignored.

If there are 5 or more contiguous, or 8 or more composite, clock hours of stage 3, the eye is still considered at Prethreshold unless plus disease develops. Once there are 5 or more contiguous, or 8 or more composite, clock hours of stage 3 ROP with plus disease present, the eye is at Threshold. An eye is considered to have plus disease if at least two of the four quadrants of the posterior pole arteriovenous pairs of vessels seen around the disc prior to initiating scleral depression have dilatation AND tortuosity that meets or exceeds the degree shown in the standard photographs. Refer to Appendix I for standard photographs of plus disease.

Areas of neovascularization must be attached to a ROP ridge to be considered stage 3 disease. If these areas are not attached, they should be considered to be "popcorn lesions of stage 2" even if they are banded together.

**Zone 2: Stage 2+.** If plus disease is present with any number of clock hours of Zone 2 stage 2 ROP, or with not enough stage 3 clock hours to meet Threshold criteria, this is Prethreshold disease.

Exhibit 6-3 illustrates ROP severity by zone and stage as defined by STOP-ROP, modified from the CRYO-ROP study.
EXHIBIT 6-3

**ROP SEVERITY**

<table>
<thead>
<tr>
<th></th>
<th>No stage</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4/5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plus disease</td>
<td>N/A</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Zone 1</td>
<td>&lt;P</td>
<td>P</td>
<td>T</td>
<td>P</td>
<td>T</td>
</tr>
<tr>
<td>Zone 2</td>
<td>&lt;P</td>
<td>&lt;P</td>
<td>&lt;P</td>
<td>&lt;P</td>
<td>P</td>
</tr>
<tr>
<td>Zone 3</td>
<td>&lt;P</td>
<td>&lt;P</td>
<td>&lt;P</td>
<td>&lt;P</td>
<td>&lt;P</td>
</tr>
</tbody>
</table>

Key:

+  plus disease (at least 2 quadrants)
3+  <5 contiguous and <8 composite clock hours of stage 3 with plus disease
3++ ≥5 contiguous hours or ≥8 composite clock hours of stage 3 with plus disease
<P less than Prethreshold
P  Prethreshold
T  Threshold
>T  Beyond Threshold
Note: Zone 3 ROP. This manifestation of ROP does not meet the study's Prethreshold definition and therefore such infants will not be enrolled.

Recording Prethreshold Entry Examination Results

SPECIAL CASES: ONLY ONE EYE AT PRETHRESHOLD: If one eye is at Prethreshold and the other is not (because its ROP is either less severe OR more severe), the infant may still be randomized, based on the one eligible eye. These possibilities for the two eyes include:

- Prethreshold - No ROP (immature or mature)
- Prethreshold - less than Prethreshold ROP
- Prethreshold - Threshold ROP
- Prethreshold - ROP worse than Threshold
- Prethreshold - ROP status post cryotherapy or laser therapy

Because these combinations may occur in clinical practice, we have chosen to include them in the trial, since neither the conventional nor supplemental oxygen treatment will interfere with any other medically indicated treatment for less severe ROP (no indicated treatment) or more severe ROP (cryo or laser therapy). When only one eye is at Prethreshold at the time of randomization, both eyes will be examined on a weekly basis. The infant will remain on assigned oxygen treatment for a minimum of two weeks and until both eyes have reached ophthalmic endpoints, regardless of the fellow eye's status at entry. For example, if the fellow eye is less than Prethreshold at entry, and never progresses to Prethreshold, the eye will continue to be examined on a weekly basis until it becomes fully vascularized or in zone 3 for the second time.

6.1.2 Exclusion Criteria

Factors that will exclude potential infants from enrollment are:

1. The parents refuse consent.

2. The infant's pediatrician or neonatologist refueses.

3. The infant's lung disease is so severe that it is not possible to meet the study ranges of pulse oximetry more than half of the time. That is, the infant's median saturation is less than 96% on high ventilator pressures and 100% oxygen, or the neonatologist caring for the infant does not agree that the supplemental range can be maintained.

4. The infant has no significant lung disease, and pulse oximetry, using an Ohmeda pulse oximeter, is greater than 94% in room air more than half of the time. That is, the median saturation value exceeds 94% in room air (>95% if oximeter is a Nellcor;
Nellcor has been found to read consistently higher than Ohmeda - see Section 7.2.1.2).

There are several ways to determine if an infant on room air has pulse oximetry greater than 94% more than half of the time, that is, if the median saturation value on room air exceeds 94%. These several ways are listed in order of preference in this section. Each infant who is otherwise eligible and in room air is to be evaluated by the most preferred method among the following:

Note: Please refer to your Study Center policy regarding parental consent to place infant on pulse oximeter

a) 4-24 hours of continuous monitoring of pulse oximetry by a study oximeter and laptop computer. This will permit an objective percent of time to be determined. The laptop program has a practice/monitoring option in which the oximetry data are collected normally, but not saved to disk. This option allows monitoring of oximetry status prior to randomization. The laptop data collection program displays in the middle of the data collection screen a graph titled: "% time:4 hours". This graph uses horizontal bars to show the percent of time spent, over the past four hours, at various saturation values. The height of each bar (on the vertical axis) gives the saturation value, while the length of the bar (measured on the horizontal axis) gives the percent time spent at that saturation value. The bar corresponding to the median is identified by a dotted line drawn through it. Enter the saturation (vertical axis) value for this bar.

b) 4-8 hours of continuous monitoring of pulse oximetry on an Ohmeda oximeter with a computer printout of trends. Ohmeda 3700 and 3740 can produce such a printout. There are also commercial programs that produce such analyses based on a "dump" of continuous data. To obtain the median:

If the median is displayed, record it.

If percents of time spent at various saturation levels are displayed, calculate a median as follows: Starting from the lowest saturation value and moving upward, add together the percents time. When this sum exceeds 50, stop. The saturation value for the last percent you have added is the median. Record this value. For example, suppose the percents time at various saturation values are:

<table>
<thead>
<tr>
<th>sat</th>
<th>% time</th>
<th>sat</th>
<th>% time</th>
<th>sat</th>
<th>%time</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
<td>5</td>
<td>90</td>
<td>30</td>
<td>92</td>
<td>20</td>
</tr>
<tr>
<td>89</td>
<td>10</td>
<td>91</td>
<td>20</td>
<td>93</td>
<td>15</td>
</tr>
</tbody>
</table>

6-8
The percents for 88, 89, and 90 are $5 + 10 + 30 = 45$. Adding the percent for 91 brings the sum up to 65, so the median is 91. Notice that the median is not necessarily the most frequent value (90, in this case, with 30% of the time), nor is it equal to the average (90.85, in this case).

If the saturation values are displayed, sort them in order and record the middle saturation value as the median.

c) 4-12 hours of continuous monitoring of pulse oximetry on a pulse oximeter other than an Ohmeda, with a computer printout of summary data giving the percent time at various levels of saturation. Some oximeters can do such a printout, others have such data in memory that can be recalled (but not printed) and there are also commercial programs that produce such analyses based on a "dump" of continuous data. Obtain the median as per b). If the oximeter in question is a Nellcor, subtract 1 from the median; Nellcor consistently reads 1-2% above Ohmeda.

d) 2-4 hours of continuous monitoring analyzed as per b) with an Ohmeda.

e) 2-4 hours of continuous monitoring analyzed as per c) with a pulse oximeter other than an Ohmeda.

f) 4 hours of sitting at the bedside watching a continuous monitoring of saturation using the Ohmeda pulse oximeter. Write down the subjective "most frequent" oximetry every 5 minutes for the preceding 5 minutes. You will have 48 values. Sort them in order. Record the middle saturation value as the median.

g) 4 hours of sitting at the bedside watching a continuous monitoring of saturation using a pulse oximeter other than an Ohmeda. Write down the subjective "most frequent" oximetry every 5 minutes for the preceding 5 minutes. You will have 48 values. Sort them in order. Record the middle saturation value as the median. If using Nellcor, subtract 1% from the median.

h) If nursing staff have been determining and charting pulse oximetry in this infant on room air, take all values for the preceding 24 hours saturation. These must include at least 5 values in the 24-hour period. Sort them in order. Record the middle saturation value as the median. If using Nellcor, subtract 1% from the median.

5. A pulse oximeter is not available for full-time use at the time of the study.

[NOTE: If a pulse oximeter is not available at the Study Center, the Study Center Coordinator must immediately notify the Coordinating Center. The
Coordinating Center has available a limited number of pulse oximeters and laptops for emergency distribution and will arrange for overnight delivery of the equipment to the Study Center. A potential participant should only be excluded in the unlikely event that an oximeter is unavailable at both the Study Center and the Coordinating Center.

6. Parents are not willing to accept the chance of restarting oxygen (a particular consideration for infants already at home).

7. The infant is transferred to a non STOP-ROP institution before randomization can take place.

8. Neither eye is at Prethreshold when a certified examiner sees the infant, i.e., the ROP has regressed or passed on to Threshold.

9. Infant has a fatal congenital anomaly, or a congenital eye anomaly, or any ocular disease or condition, the presence of which may now or in the future complicate evaluation of ROP (e.g., CMV retinitis).

10. Infant is enrolled in another study that may interfere with STOP-ROP protocol requirements, or is likely to be unavailable for follow-up.

Infants who have been registered as having Prethreshold ROP in at least one eye, but who are found to meet one or more of the above exclusion criteria will be noted in the register as excluded from the study with the specific reason given. In the register, all Prethreshold infants will have a final entry of treatment assignment (C for conventional, S for supplemental), or a coded reason for exclusion.

6.2 SOURCES OF INFANTS

Infants in a Study Center's NICU may become eligible for enrollment if they reach Prethreshold ROP. In addition, infants may also be referred from other institutions which do not function as participating Study Centers as long as at least one eye is confirmed by a STOP-ROP certified ophthalmologist to be at Prethreshold.

6.3 CONSENT

When an infant begins to develop significant ROP (see 6.1.1) that has not met Prethreshold criteria, the SCC should begin discussing the possibility of participating in STOP-ROP with the child's parents or guardians. An information leaflet and a copy of the consent form should be distributed so that parents may have an opportunity to have their questions answered and to discuss the study with their pediatrician before it is actually necessary to make a decision regarding enrollment. A copy of the information leaflet and consent form may be found in Appendices D and E. A videotaped description of the study will also be available to use in obtaining informed consent.
The PI may request that the SCC obtain the informed consent. In such cases, the PI will also sign the consent form to endorse it and to assure availability of the PI to the parents. Consent should be obtained from both parents. If, following randomization, the designated legal guardian changes, a new informed consent must be obtained from the current legal guardian.

6.4 INITIAL DATA COLLECTION: Entry requires two exams

When an examiner first determines that an infant has Prethreshold disease, no data forms will have been completed as yet. Demographic and identifying information for the Patient Register (Section 6.1) is collected at this time, and consent is obtained. The enrollment eye exam is then performed by an examiner, other than the first examiner, to confirm eligibility. At least one of the examiners must be a study certified ophthalmologist. If both examiners are certified, either may complete the Retinal Examination form, provided that the interval between the two exams is no greater than 48 hours. If the interval exceeds 48 hours, the second examiner must complete the Retinal Examination form. The date and time of each exam, the names and certification numbers (if applicable) of the examining ophthalmologists, and a summary of the results from a certified examiner are recorded on the Baseline, Eligibility and Randomization form (STOP 01). The confirming examination should be scheduled within 24 hours of the initial Prethreshold exam. If neither eye can be confirmed by the certified examiner to meet Prethreshold criteria, weekly examinations resume until enrollment criteria are met or the ROP regresses. If regression occurs without either eye reaching Prethreshold, the infant will then be documented in the register as having been excluded from the study, with the reason noted.

6.5 REGISTRATION, STRATIFICATION AND RANDOMIZATION

The unit of study in STOP-ROP is the infant. An infant is enrolled in STOP-ROP as soon as he or she is randomized. Registration and randomization will be transacted on the telephone between the Study Center Coordinator and Data Coordinator at the Coordinating Center. The Study Center Coordinator will verify that all eligibility criteria are met by calling the Coordinating Center at 301/299-8655 between 9:00 AM and 5:00 PM (EST) Monday through Friday (see below for after hours). At the time of the call, the Baseline, Eligibility and Randomization form (STOP 01) must be completed with the results of the study-certified Prethreshold exam recorded on the Retinal Examination form (STOP 02), the date and time of the certified examination, the infant's birth weight, and a checklist of exclusion criteria. The Coordinating Center will promptly register and randomize a patient after verbally reviewing this form with the SCC and confirming that all eligibility criteria, including the signing of the consent form, have been met. The Coordinating Center will randomly assign the infant to either conventional or supplemental oxygen, and therapy should begin immediately.
THE GOAL IS TO BEGIN THE ASSIGNED OXYGEN TREATMENT WITHIN 24 HOURS OF MAKING THE DIAGNOSIS OF PRETHRESHOLD ROP. If more than 24 hours pass from initial diagnosis of Prethreshold ROP to randomization, the infant may still be randomized, but will be designated a "Late Entrant" (see Section 6.6.1).

6.5.1 Stratification

Randomization will be stratified on the severity of the Prethreshold disease. The purpose of stratified entry is to balance severity within treatment groups and NOT to test for statistically significant difference within subgroups. Two strata are defined for STOP-ROP:

**ONE EYE**

A. High severity
   Prethreshold ROP any zone
   Prethreshold ROP zone 1

B. Low severity
   Prethreshold ROP zone 2
   Prethreshold ROP any zone

**FELLOW EYE**

Worse than Prethreshold (any zone)
Prethreshold ROP any zone
Prethreshold ROP zone 2
Less than Prethreshold ROP
(includes no ROP)

The strata will be determined by the SCC following review of the ophthalmic summary on the Retinal Examination form (STOP 02).

6.5.2 Randomization

Treatments are assigned in random order by the Coordinating Center, and sets of treatment assignments are distributed to each Study Center in sealed envelopes. The envelopes will be sealed with strong glue to prevent possible unobtrusive opening and resealing. Each randomization set will consist of a series of sealed envelopes, sequentially numbered within strata. On the outside of each envelope will be the stratification identification, sequence number, and the 2-digit Study Center code. During the telephone call to the Coordinating Center to randomize an infant, the Coordinating Center will ask the Study Center Coordinator to open the envelope corresponding to the stratification code and lowest sequence number within the stratum. Within the sealed envelope will be a folded, postcard size, two-part, tear-apart card imprinted on one half with the treatment arm designation and a space for recording the 3-digit patient number. The other half will be imprinted with the Coordinating Center's address. The SCC will record the date and time of randomization, hospital code, patient number, and name and certification number of person enrolling the participant on each section of the tear-apart card and mail one card.
to the Coordinating Center and retain the other half in the infant's study chart. The SCC will then record the 7-digit STOP-ROP Identification number on the appropriate sequence line of the Randomization Log corresponding to the proper stratum.

The STOP-ROP identification number is a 7-digit number and is the permanent, unique STOP-ROP identification number assigned to each enrolled participant. The first two digits of the STOP-ROP identification number represent the Study Center number assigned to each Study Center at the beginning of the study, the next two digits represent the hospital code assigned at the beginning of the study, and the last three digits represent the participant number assigned at the time of randomization. Specifically, for enrolled patients that have not been transferred, the participant number is the sequential number of the patient within the Study Center. This can range from 001 to 199.

In addition, each participant will be identified by a name code and hospital ID number. The name code is six letters in length and includes, in order, the first three letters of the participant's last name, the first two letters of the first name, and the first letter of the middle name. If the last name is 2 letters, an "X" will be used for the third letter. When the infant has a hyphenated last name (e.g. Gonzales-Ramirez), use the first 3 letters of the first component of the last name (e.g. GON). If the participant has no first or middle name, X's are used in place of a first name or middle initial. The hospital ID number is the medical record number issued to the participant at the time of birth. Once the identification number is assigned, it remains with the participant throughout the study, unless the participant is transferred from one Study Center to another Study Center; this would change his/her 7-digit STOP-ROP identifier. Specifically, a transferred patient receives a new center number, hospital code and participant number from 901 to 999.

Neonatal Network Centers will use their 4-digit Network number and 2-digit Network Center number in addition to the STOP-ROP identifiers on all data forms.

6.5.3 Randomization when the Coordinating Center cannot be reached

When the Coordinating Center cannot be reached by telephone, randomization will be accomplished by means of the sealed envelopes alone. The Study Center Coordinator will follow this procedure:

1. Complete relevant forms before randomization

Verify that the Baseline, Eligibility and Randomization form (STOP 01) questions 1-13 and the Retinal Examination form (STOP 02) ophthalmic summary (question 7) have been completed before attempting randomization. In particular, STOP 01 question 13 should indicate that the infant is eligible for randomization. That is, parts a-d must be answered Yes, and either e or f must be answered Yes.
2. **Determine the new participant number**

   Find the greater of the last participant number in the stratum A log and the last participant number in the stratum B log (REMEMBER TO LOOK AT BOTH LOGS TO DETERMINE THE LAST NUMBER USED). Add one to the number found to get the new participant number (which will be the last three digits of the STOP-ROP ID Number).

3. **Determine the stratum**

   Determine the infant's stratum by considering Question #7 on the Ophthalmic summary from the Retinal Examination form (STOP 02) in conjunction with the ROP Severity Table and stratum definition box on page 3 of the Baseline, Eligibility and Randomization form (STOP 01).

4. **Determine the sequence number**

   Locate the next available sequence number on the randomization log of the appropriate stratum.

5. **Determine treatment assignment: open envelopes**

   Verify that the next available envelope in the box of the appropriate stratum has a sequence number that matches the sequence number you have just determined. Also, verify that the center number matches your center number.

   Fill out the eligibility checklist on the outside of the envelope.

   Open the envelope and verify that the stratum and sequence number of the inside envelope matches that of the outside envelope. Also, verify that the center number matches your center number.

   Write the hospital code (2 digits) and the participant number (3 digits) on the outside envelope. Together these two fields comprise the last 5 digits of the STOP-ROP ID number.

   Open the inside envelope to obtain the two part, tear-apart card. Verify stratum and sequence number on the card. Also, verify that the center number matches your center number.

6. **Fill out tear-apart card**

   Record the date and time of randomization, hospital code, participant number, and your name and certification number on each section of the tear-apart card. Mail
one card to the Coordinating Center and retain the other, and the envelopes, in the
infant's study file. The date and time of randomization is the date and time when
the randomization envelope is opened. The first weekly visit post-randomization
should take place 4-10 days after randomization.

7. **Fill out Randomization Log**

Record the 7-digit STOP-ROP ID Number on the appropriate sequence line of the
Study Center Randomization Log. *Note*: Be sure that the Log you are using is the
one that corresponds to the correct stratum of the infant's eye.

8. **Complete Patient Register**

Complete Question #15 (Treatment Assignment) on the Patient Register (STOP 00)
form.

9. **Telephone Coordinating Center**

Telephone the Coordinating Center at 301/299-8659 and provide the following
information for the telephone answering machine:

- today's date and time of call
- infant's name code and registration number
- eligibility information requested
- treatment assignment

10. **Complete Baseline, Eligibility and Randomization Form**

The Baseline, Eligibility and Randomization form (STOP 01) should already have
been completed up to question 13 before attempting to randomize. Now complete
up to question 19 and fax to the Coordinating Center within 24 hours of
randomization.

At 8, 16, and 24 hours after randomization, complete question #20 on the Baseline,
Eligibility and Randomization form (STOP 01). When complete, mail original to the
Coordinating Center.

Place the completed Baseline, Eligibility and Randomization form (STOP 01) and
the Retinal Examination form (STOP 02) in the infant's STOP-ROP file.
11. **Receive Infant Examination Schedule**

   The Coordinating Center will fax you a copy of the STOP-ROP Schedule of Post-randomization Examinations for this infant. On the cover memo used to fax this schedule, the most current information entered in the Coordinating Center Randomization Logs will be written. **CHECK THIS INFORMATION (PARTICIPANT NUMBER, STRATUM, AND SEQUENCE NUMBER) AGAINST YOUR STUDY CENTER'S RANDOMIZATION LOGS.** If there are any discrepancies, call the STOP-ROP Coordinating Center at 301/299-8655 during normal business hours.

6.6  **SPECIAL CASES**

6.6.1 **Late Entry**

   If more than 24 hours pass from the initial diagnosis of Prethreshold ROP to randomization, the infant may still be randomized, but will be designated a "Late Entrant." Initial diagnosis occurs the first time the infant is identified as having Prethreshold ROP (by STOP-ROP definitions) in a STOP-ROP institution. The initial diagnosis can be made by a non-study-certified ophthalmologist or a study-certified ophthalmologist. The initial diagnosis must be confirmed, and there can be no unresolved intervening dissenting diagnosis by a certified ophthalmologist. If more than 48 hours have elapsed from the last exam by a certified ophthalmologist, a repeat eye examination by a certified ophthalmologist must document current continued eligibility prior to randomization.

6.7 **PROCEDURES FOLLOWING RANDOMIZATION**

   Following the completion of the randomization procedure, the infant is assigned to an oxygen treatment arm of either conventional or supplemental oxygen and must be maintained on this oxygen treatment and study equipment for a minimum of two weeks. If both eyes progress to confirmed Threshold during that time, the assigned oxygen treatment will revert to routine management after the two weeks. If one eye remains less than Threshold, the infant will continue on the assigned treatment and study equipment until the ROP progresses to Threshold or beyond, or regresses to zone 3. The process associated with STOP-ROP data forms to be completed, examinations to be performed, and monitoring data to be collected during the entire phase of the study is summarized below, while details on form completion are available in the Data Management Handbook.
6.7.1 Oxygen Management

Prior to randomization on the Baseline, Eligibility and Randomization form (STOP 01). The same data will be recorded eight, sixteen, and thirty-two hours post randomization. These data will provide a description of the changes in infant management required to adhere to the assigned treatment. The Ohmeda pulse oximeter, Oxytip neonatal probes, and a laptop computer will be used to monitor saturation data (Chapter 7). Saturation data will be stored on computer disk until the infant has reached assigned oxygen treatment for a minimum of two weeks and until both sets have been sent to the Coordinating Center. The disk should be labeled "final."

6.7.2 Weekly During Oxygen Treatment

A STOP-ROP certified ophthalmologist masked to oxygen treatment assignment will perform an ophthalmic examination and a summary of the results will be recorded by the SCC on the Weekly Outcome form (STOP 03). The certified ophthalmologist may decide that the clinical status of the infant requires an examination more often than weekly. The additional examination(s) should not be documented on the Weekly Outcome form(s). The window for weekly examinations is ±3 days (e.g. the first weekly examination after randomization [= day 0] will occur between day 4 and day 10). If a randomized infant is deemed to be too medically unstable to undergo eye examinations, it is acceptable to reschedule examinations for the next possible date. If the examination is not performed within the examination window, a Protocol Anomaly form (STOP 06) is completed by the Study Center Coordinator and the reason for a missed visit documented. A neonatologist should document the reason why the examination was not performed in the infant's medical record.

When an eye reaches an adverse or favorable endpoint for the first time, a Retinal Examination form (STOP 02) must be completed and submitted by the certified ophthalmologist. Weekly eye examinations will continue during oxygen treatment until an endpoint is reached in each eye. In general, both eyes must be examined at weekly examinations and assigned oxygen treatment will continue until each eye has reached an endpoint (Threshold or beyond, vessels extended into Zone 3 for the second consecutive weekly examination, or fully vascularized). There is one exception: no further examination of a fully vascularized eye is required, even if weekly examinations and assigned oxygen treatment are to continue because the fellow eye is not at endpoint. An endpoint is reached when regression in zone 3 is established in 2 successive examinations, or Threshold disease or beyond is established and confirmed by a certified ophthalmologist, or vessels are fully vascularized. In the rare event (e.g. unexpected absence or illness) a masked certified examiner is not available, an unmasked certified examiner may be used. If a certified examiner is not available, then a masked examiner, not certified for STOP-ROP, may be used. If an uncertified examiner completes a form, code the two-digit STOP-
ROP center number followed by 99 as the 4-digit certification number for the examiner. If the only examiner available is an unmasked, uncertified examiner and the examination cannot be rescheduled, the exam should still take place and the information recorded on the form.

If one eye is at or beyond Threshold, while the fellow eye is not, some ophthalmologists will elect to treat both eyes simultaneously, to avoid delay, cause less stress, and spare the infant anesthesia. While the STOP-ROP study cannot dictate clinical practice, it is a Protocol Anomaly to treat both eyes when only one is at Threshold. Ophthalmologists confronted with such a scenario are asked to call the Study Chair, an ophthalmologist on the Executive Committee, or the Coordinating Center, to provide details of the ophthalmic findings prior to surgery. If the call is not possible because of the timing of surgery, a call to explain the circumstances must be made as soon as possible following surgery. In addition, a Protocol Anomaly form must be completed and submitted to document the case.

Other data to be collected on the Weekly Outcome form (STOP 03) include measurements of head circumference, length and weight, description of oxygen management, saturation values, apnea assessment and occurrences of adverse experiences including seizures, pneumonia, necrotizing enterocolitis, hypoxia and hyperoxia.

6.7.3 Initial Discharge to Home

An Initial Discharge form (STOP 10) must be completed when an infant is initially discharged home. The Parent/Caretaker Interview (STOP 10A) form may also be required on initial discharge. The cost-effectiveness analysis described in section 1.5 requires an estimate of the socioeconomic status of each family participating in the study. This is used as a proxy measure to investigate whether, at the time of discharge, the ability of the infant's family to take the infant home on study equipment is the same in the two treatment groups. The STOP 10A form has been designed to answer this question. This form is completed, in person or over the phone, by the Study Center Coordinator with the family at the time of initial discharge or the 3-month neonatal examination, whichever comes first. In rare circumstances, a Study Center Coordinator may determine that a family is so sensitive about the questions asked in the STOP 10A form that obtaining the answers at the time of initial discharge may jeopardize further follow-up of the infant. In these cases the Study Center Coordinator may, upon informing the Coordinating Center by writing, postpone completion of the STOP 10A until the 3-month neonatal examination, even if initial discharge occurs first. The questions on the STOP 10A form should be asked of the infant's father and mother, who live together with the infant. This may not be possible in all cases. If there are two or more adults in the home who are actually responsible for the infant, take the data from the two most closely approximating "parents." See the Data Management Handbook for additional instructions.
Rehospitalization forms (STOP 11) must be completed each time the infant is readmitted and discharged. If the infant has not reached a study endpoint in each eye at the time of discharge (Section 8.3), weekly eye examinations must be continued and the Weekly Outcome form (STOP 03) completed. If both eyes have reached study endpoints no further visits are required until the 3-month corrected age follow-up visit.

6.7.4 3-month (corrected age) Follow-up

All randomized infants will be examined 10-14 weeks post due date. Examinations that occur within this time frame are considered to be within the examination window. If it proves impossible to perform the examination within the window, it should be performed as close to the window as possible.

EXAMPLE: An infant is born at 28 weeks gestation. 12 weeks post due date would be 24 weeks later. [40 weeks is when the infant would have been born if he or she was born at full term. Therefore the three-month exam is done at 10-14 weeks after the infant's original due date for delivery.]

A STOP-ROP certified ophthalmologist masked to oxygen treatment will perform an ophthalmic examination and complete a Three-Month Ophthalmic Outcome Examination form (STOP 04). As with the weekly examinations, if a masked, certified examiner is not available and the 3-month exam cannot be rescheduled, the order of preference for examiners is:

- unmasked, certified
- masked, uncertified
- unmasked, uncertified.

Rarely, an infant may not attain ophthalmic endpoints at the three-month corrected age examination. In this circumstance, three-month examinations should be completed on target and study equipment discontinued. The final diskette and study forms should be submitted to the Coordinating Center. Two weeks after receipt of three-month examination forms, the Coordinating Center will mail the Six Month Ophthalmic Outcome form (STOP 04A) to the Study Center Coordinator. When the infant reaches ophthalmic endpoints in both eyes, or six months corrected age, whichever is earlier, the examining ophthalmologist (certified preferred) should complete the Six Month Ophthalmic Outcome Form (STOP 04A).

The neonatologist will assist the SCC in the completion of the Three-Month Neonatal Outcome form (STOP 05) to document the infant's neonatal development status. The infant's parents will be asked to complete the Revised Denver Developmental
Questionnaire (STOP 09) with assistance from the SCC. In addition, the Parent/Caretaker Interview (STOP 10A) should be completed if previously not submitted.

6.8 NURSING SUPPORT SERVICES

The skills, knowledge, and enthusiasm of the NICU nurses are critical to the success of this study. Neonatologists, Ophthalmologists, and Study Center Coordinators should provide ongoing support and education to assure their maximum cooperation and enthusiasm in this research effort. In addition to such support given by individual Study Centers, periodic newsletters will be produced at the Coordinating Center and distributed to all participants to promote a sense of joint cooperation and group identity.

6.9 MAINTAINING CONTACT WITH FAMILIES

Infants who develop ROP have a disease that generates a great deal of anxiety and concern to their parents. STOP-ROP physicians, SCCs, and nursing staff are in an excellent position to reduce their anxieties by providing critical information in a timely manner, and through the establishment of mutual bonds of trust and cooperation. The effort and time invested in building mutual trust and cooperation will be necessary to maintain contact with families following discharge of their infant to the home environment. In order to secure their continued support and return for all post-discharge examinations, the following techniques have been found to be useful in this process:

1. Assist the parents in applying for the infant’s Social Security Number.

2. Inform parents promptly about the results of each eye examination and when the next one is scheduled.

3. Obtain phone numbers and addresses for the infant’s parents, grandparents, aunts, uncles or any other significant family members.

4. Obtain name and phone number of the pediatrician and other physicians who will be following the infant after discharge.

5. Establish an educational and information network with the admission clerks and physicians at referring hospitals to which infants are back transferred. Request that the neonatologist investigator receive a copy of the infant's discharge summary at the time of discharge from any stepdown unit to which the infant may have been transferred.

6. Reimburse families for the costs of parking, gas, babysitters, and time when they return to clinic for the 3-month visit.
7. Study staff should be familiar with the administration procedures at the individual study center in order to direct families to the appropriate persons when problems are encountered. Such individuals available for help may be primary nurses, social workers, financial counselors, ombudsmen, parent support groups, etc.
CHAPTER 7

OXYGEN THERAPY AND PATIENT MANAGEMENT
CHAPTER 7

OXYGEN THERAPY AND PATIENT MANAGEMENT

The STOP-ROP study depends on the application of one of two strategies of administering oxygen to premature infants. Both approaches must be sufficiently precise to allow scientific conclusions to be based on their application, yet at the same time simple enough to permit intensive care nurseries to apply them to future populations, should the study results be positive and supplemental oxygen safe. This chapter will define the two strategies and detail the methods by which the study will facilitate their application in actual nursery settings.

7.1 DEFINITIONS OF OXYGEN TREATMENT

7.1.1 Background

In the Neonatal Intensive Care Units (NICUs) of the 1990’s, oxygen administration is monitored with a variety of techniques, each associated with its own risks and values:

**Direct:**
- Intermittent: Arterial PaO₂
  - Capillary Blood Sampling
  - Venous Blood Sampling
- Continuous: Indwelling Arterial Line PaO₂ Lines

**Indirect:**
- Transcutaneous PaO₂
- Pulse Oximetry Saturation

Only the last of these, pulse oximetry, remains sufficiently free of risk and reasonably reliable as infants grow older and their skin thickens and matures. The direct techniques of measurement carry risks of infection and thrombosis and are not justified after the first several days to weeks of life as the infant stabilizes. Transcutaneous PaO₂ measurements are relatively good for determining trends, but are not related in a consistent manner to arterial PaO₂ values as the infant becomes older and the skin thickens. Also, these monitors must be heated to 44 degrees centigrade and can cause burns. Pulse oximetry gives a quick, reliable, and relatively risk-free measurement of actual arterial oxygen saturation.

The significant drawback of pulse oximetry is that the infant’s hemoglobin becomes fully saturated (100%) at an arterial PaO₂ of about 85-120 torr, and thereafter cannot exceed 100%, even if the arterial PaO₂ continues to climb to 200 or greater torr. This concern is addressed in this chapter. While it is a potential problem for the study, we believe the data show the study goals can be accomplished.
At the opposite end of the spectrum, the lower limits of safe saturation for a premature infant have not been defined, and it is not known at what level pulmonary hypertension occurs, nor hypoxic cerebral injury.

7.1.2 Conventional Oxygen Strategy: Pulse Oximetry of 89-94%  

The opinions of 406 of the 605 (67%) NICUs in the USA regarding oxygen administration and monitoring were obtained through a questionnaire distributed in 1988 (32). The results revealed that most NICUs do not measure the pulse oximetry of infants who are not receiving oxygen, and for infants who are receiving oxygen, the oxygen given is adjusted to maintain a variety of pulse oximetry readings (Exhibit 7-1). The majority, however, attempt to maintain a pulse oximetry between 90-95% saturation, and this corresponds to an arterial PaO₂ value of 45-85 torr 90% of the time (33).

For STOP-ROP: The Conventional O₂ strategy will be to maintain the pulse oximetry saturation from 89-94%, inclusive, at least 50% of the time. This mode of oxygen treatment is presently the most commonly used approach, and presents no change in risk.

7.1.3 Supplemental Oxygen Strategy: Pulse Oximetry of 96-99%  

The goal of the supplemental oxygen strategy will be to minimize periods of hypoxemia and to maintain average oxygenation at levels that will supply the peripheral retina with sufficient oxygen to depress the release of putative angiogenic growth factors (16,24).

For STOP-ROP: Supplemental oxygen will be defined as a pulse oximetry saturation range of 96-99%, inclusive, at least 50% of the time. This will correspond to an arterial PaO₂ of 64-109 torr at least 90% of the time that the infant is within the given target range (33).

7.2 STANDARDIZATION OF PULSE OXIMETER  

7.2.1 Background  

A survey of potential participating centers revealed that the two pulse oximeters most commonly used are the Nellcor and the Ohmeda. Therefore both of these instruments were evaluated during the planning phase.
**EXHIBIT 7-1**

**SUMMARY OF RESULTS FROM OXYGEN ADMINISTRATION SURVEY**

<table>
<thead>
<tr>
<th>Minimum Saturation Criteria</th>
<th>(n=168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 85%</td>
<td>32 (19% of responders)</td>
</tr>
<tr>
<td>Over 88%</td>
<td>29 (17%)</td>
</tr>
<tr>
<td>Over 90%</td>
<td>79 (47%)</td>
</tr>
<tr>
<td>Over 92%</td>
<td>20 (12%)</td>
</tr>
<tr>
<td>Over 94%</td>
<td>5 (03%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (02%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maximum Saturation Criteria</th>
<th>(n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 94%</td>
<td>32 (24%)</td>
</tr>
<tr>
<td>Under 96%</td>
<td>52 (40%)</td>
</tr>
<tr>
<td>Under 97%</td>
<td>7 (05%)</td>
</tr>
<tr>
<td>Under 98%</td>
<td>13 (10%)</td>
</tr>
<tr>
<td>Under 99%</td>
<td>3 (02%)</td>
</tr>
<tr>
<td>Under 100%</td>
<td>4 (03%)</td>
</tr>
<tr>
<td>No Upper Limit</td>
<td>20 (15%)</td>
</tr>
</tbody>
</table>

* Phelps DL and Colf N (32)
7.2.1.1 *Comparisons of pulse oximeters as a surrogate for arterial oxygen saturation.*
The ability of 14 pulse oximeters to serve as a surrogate for monitoring arterial oxygen saturation (SaO₂) was recently reported [34]. The Nellcor-N200, Ohmeda-Biox 3700 and Ohmeda-Biox 3740 were included in the study. The study found that in the range of saturation to be studied by STOP-ROP (89%-99%) the Ohmeda 3740 was ranked among the top 4 in measures of error in accuracy (mean difference between SpO₂ and SaO₂), precision (root mean squared difference between SpO₂ and SaO₂), and an index of agreement between the two measures (correlation coefficient of Bartko [35]). All three instruments were ranked within the top 7 for each of these measures.

7.2.1.2 *Comparison of Nellcor vs. Ohmeda.* The Nellcor and Ohmeda pulse oximeters were evaluated during the planning phase to determine the necessity for standardization of the choice of oximeter for STOP-ROP.

**Saturation readings.** A systematic difference between the saturation readings of the Ohmeda and Nellcor oximeters has been reported by the manufacturers. This difference is a result of the correction of the saturation readings for the presence of 1.6% carboxy hemoglobin and 0.4% methemoglobin in the blood by the Ohmeda oximeter. When no correction is applied (Nellcor), the pulse oximetry reads about 2% higher than when a correction is performed [see Ohmeda Product Data, Appendix G]. As a consequence, infants on a Nellcor Oximeter have readings of 100% saturation far more often than infants who are being monitored with the Ohmeda pulse oximeter. We monitored 2 infants with both instruments simultaneously over four 3 to 6 hour sessions each and confirmed this consistent difference between the readings from these two instruments. The distribution of Nellcor saturation readings were consistently higher than the Ohmeda readings at each of the 25th, 50th, and 75th percentiles. This difference was observed in each of the four sessions for each of the two infants.

The difference observed on 120 simultaneous samples (Nellcor, Ohmeda and arterial sample) was that the Ohmeda readings were 1.6±2.7 (M±SD) below the Nellcor. On these 120 samples, pO₂ is <100[torr] if SpO₂ is <98%. Also, pO₂ is >50 if SpO₂ is >90% for the Ohmeda or >92% for the Nellcor in most cases. [36]

**Use.** Both instruments proved moderately easy to learn to use. The red digital readout of the Nellcor was somewhat easier to read, but the liquid crystal display on the Ohmeda was sufficiently clear (particularly with the rheostat adjustment) to permit easy use. In addition, the Ohmeda has the ability to display the previous 20 min. or 60 min. of oximetry tracing for the review of the staff taking care of the infant. This would prove useful in the event of a malfunction or delay of availability of the laptop for monitoring pulse oximetry [see section 7.3].

7.2.2 *Pulse Oximeter to be used in STOP-ROP*

The systematic differences in the Nellcor and Ohmeda pulse oximeter necessitate the choice of one brand of oximeter for study infants. The Ohmeda 3740 Pulse Oximeter
and Oxytip Neonatal Probes will be used in STOP-ROP to monitor study infants. Once an infant is enrolled, the Oxytip oximeter probes should be changed every seven days. Any problems that occur before seven days should be reported to the Coordinating Center. These problems may lead to changes in policy. Such changes will be communicated by the Coordinating Center to the Study Centers. Each Study Center will be provided with at least one pulse oximeter that will be dedicated to study infants. Backup pulse oximeters will be made available through the Coordinating Center on 24 hours notice as additional infants are enrolled.

7.3 SATURATION MONITORING

7.3.1 Background

A survey of participants revealed serious concerns about the ability of the NICU staff to maintain infants in the desired range all of the time. It is recognized that infants are highly variable and do not maintain their oxygen saturations at a stable level. The goal is to keep the infants in the desired range a majority (> 50%) of the time. In addition to the infants’ inherent variability, there is also an artifactual variability in monitoring continuous pulse oximetry. The latter problem is that infants move and curl their toes and fingers and otherwise disturb the ability of the probe to make accurate readings. Because of this, the oximeter often reports falsely low values because of the infant’s movement rather than because the saturation is truly low. This is the reason that we feel 50% of reporting time is sufficient to assure that the infant is in this range a majority of the time.

To study this variability and to measure and improve our ability to monitor the infants, a pilot study was conducted to assess the ability of four centers to maintain enrolled infants in the desired range. This section describes the monitoring device used and the results of the pilot.

7.3.1.1 Monitoring device. A commercial software program (Profox for the Bedside by Profox Inc.) was initially used to monitor saturation. This software allows the examination of an 8-12 hour mean distribution of the pulse oximetry from a monitored infant. The program was used to test the ability of NICU nurses to maintain infants in a range of pulse oximetry as ordered by the physician under normal circumstances.

A customized version of the Profox Software Program was next developed to act in concert with an inexpensive laptop computer which was programmed to provide nurses with continuous feedback on how well the infant was maintained within the desired range. A comparison of monitoring results with and without the laptop demonstrated decreased variability in maintaining an infant in the desired range when nurses used the laptop. Four infants were studied. Using the laptop for assistance, nurses were able to maintain all 4 infants in the targeted range 50 to 55 percent of the time. Without the aid of the laptop, the targeted ranges were maintained above 50 percent in only two of the infants, varying from 38 percent to 60 percent time within target among the four infants.
7.3.1.2 Pilot results of saturation monitoring. The ability of NICU staff to maintain infants in the study targets was tested in 19 infants from 4 institutions: Southwestern Medical Center (Parkland Hospital and St. Paul), University of Colorado Health Sciences Center, and Strong Children’s Medical Center-Rochester. Eight of the 9 infants participating from Strong Children’s Medical Center had Prethreshold ROP and were randomly assigned to receive either conventional oxygen or supplemental oxygen therapy. Both infants from the University of Colorado received conventional oxygen, and 2 of the 8 infants enrolled by Southwestern Medical Center were assigned to supplemental oxygen based on potential benefit from a high oxygen saturation goal (e.g. persistent pulmonary hypertension of the newborn). A total of 13 infants received conventional oxygen and 6 infants received supplemental oxygen. Infants may have been on nasal cannula oxygen, hood oxygen, nasal continuous positive airway pressure, or a ventilator. Both the Ohmeda and Nellcor were used for monitoring during these pilot studies. A summary of infant characteristics by assigned therapy is provided in Exhibit 7-2.

The physician’s orders for infants in the conventional oxygen group were to wean, gradually decreasing the oxygen if the pulse oximetry was greater than 94%. Conversely, the administered oxygen was to be increased if the pulse oximetry was less than 89%. The physician’s orders for infants in the supplemental oxygen group were to wean, gradually decreasing the oxygen if the pulse oximetry was 100%. Conversely, the administered oxygen was to be increased if the pulse oximetry was less than 96%.

Ten minute average \( \text{SaO}_2 \) values were calculated for each of the 19 infants. Each infant contributed data for at least one 8 hour session (i.e. 8 hours x 6 10-minutes averages per hour = 48 data points) and not more than three 8 hour sessions. The timing of each session was dependent on staff availability. When more than 1 session was submitted, contiguous 8 hour sessions were included in the pilot database if available. Exhibit 7-3 summarizes the distribution of the ten minute average \( \text{SaO}_2 \) values by oxygen group. Infants assigned to conventional oxygen were maintained in the conventional saturation range (89.0 to 94.5) 64.7% of the time under observation. Infants assigned to supplemental oxygen remained at saturations greater than 95.5 for 59.8% of the time. In the supplemental oxygen group, infants were at saturations of 98.7 or less 95% of the time. These data suggest that nursing staff will be able to maintain infants in the targeted range more than 50% of the time without excessive periods at 100% saturation. These data are also shown graphically in Exhibit 7-4.
EXHIBIT 7-2

SUMMARY OF PATIENT CHARACTERISTICS
ASSIGNED OXYGEN LEVEL

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Conventional (n=13)</th>
<th>Supplemental (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rochester</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Parkland</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>St. Paul</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Denver</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Percent female</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Percent white</td>
<td>42</td>
<td>80</td>
</tr>
<tr>
<td>Median birthweight</td>
<td>755 grams</td>
<td>2,325 grams</td>
</tr>
<tr>
<td>Median gestational age</td>
<td>26 weeks</td>
<td>32 weeks</td>
</tr>
<tr>
<td>Median chronologic age</td>
<td>56 days</td>
<td>39 days</td>
</tr>
</tbody>
</table>
### EXHIBIT 7-3

**SUMMARY OF PILOT STUDY RESULTS BY OXYGEN GROUP USING 10 MINUTE AVERAGE \(\text{SaO}_2\) VALUES**

<table>
<thead>
<tr>
<th>Item</th>
<th>Conventional Average % (n=13)</th>
<th>Supplemental Average % (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{SaO}_2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;89.0</td>
<td>13.0</td>
<td>6.4</td>
</tr>
<tr>
<td>(\geq 89.0) and (\leq 94.5)</td>
<td>64.7</td>
<td>24.3</td>
</tr>
<tr>
<td>&gt;94.5 and (\leq 95.5)</td>
<td>9.1</td>
<td>9.5</td>
</tr>
<tr>
<td>&gt;95.5</td>
<td>13.22</td>
<td>59.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Average (\text{SaO}_2)</th>
<th>Average (\text{SaO}_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 (median)</td>
<td>92.4</td>
<td>96.2</td>
</tr>
<tr>
<td>75</td>
<td>94.1</td>
<td>97.5</td>
</tr>
<tr>
<td>90</td>
<td>95.5</td>
<td>98.3</td>
</tr>
<tr>
<td>95</td>
<td>96.4</td>
<td>98.7</td>
</tr>
</tbody>
</table>
Data from 19 infants monitored with a lap-top computer feedback system in either Conventional Oxygen (n=13) or Supplemental Oxygen Modes (n=6). These data are also expressed in a table in Exhibit 7-3 and this graph shows the separation of the oxygen exposures in these two groups. The area of overlap, while significant, fails to disguise the real separation of the oxygen exposures in these two groups. The area of overlap, while significant, fails to disguise the real separation of these two treatment modalities. See text in 7.3.1.2 for additional details.
7.3.2 Saturation Monitoring in STOP-ROP

7.3.2.1 Description of laptop monitoring system. The customized version of the Profox Software Program will be used to monitor saturation levels in STOP-ROP. The computer obtains the pulse oximeter readings every two seconds and the saturation values are plotted to the side of the screen in a simulation of a strip chart, allowing the physicians and nurses to easily view the previous one hour of tracing. A mean of the prior 10 minutes is updated every two seconds, and the mean of the prior 60 minutes is updated every 5 minutes and printed on the screen digitally (10 min and 60 min). Histograms of the frequency distribution (the preceding 20 minutes and preceding 4 hours) are updated every 1 minute and 5 minutes, respectively. See Exhibit 7-5 for a demonstration of the screen on the laptop. In order to facilitate the nurse’s abilities to maintain an infant in the desired range, the two histograms provided on the screen contain a window of the targeted range and show the percentage of time in the preceding 20 minutes and preceding 4 hours that the infant has been in the targeted range.

The pulse oximetry data are saved to disk for storage on each infant until both eyes have reached an endpoint and the infant has received assigned oxygen treatment for a minimum of 2 weeks. This will permit later analysis of the success each infant has experienced in maintaining the desired pulse oximetry.

7.3.2.2 Physician’s orders. When an infant is randomized to conventional oxygen, the nurses will receive standard orders to maintain a saturation of 89-94%, and the infant will be continuously monitored with the study-assigned pulse oximeter and computer.

When an infant is randomized to receive supplemental oxygen, the orders will read to adjust the child’s oxygen to maintain a saturation of 96-99%. These infants will also be continuously monitored via a study pulse oximeter and computer. This continual monitoring of both conventional and supplemental groups will last until the infant is discharged from his/her assigned treatment arm as described in Chapter 9, Definition of Outcome Measures. Treatment will be continued for at least 2 weeks and then will be discontinued when the infant reaches a favorable or unfavorable study outcome.

7.3.2.3 Recording and nurses’ instructions. In an Intensive Care Nursery, it is common for a pulse oximeter to be shared by different patients since there are usually not enough oximeters to go around. Data gathered from an oximeter which has recorded from several different infants overnight is not useful for study purposes. Thus, it is critical that the pulse oximeters and laptops made available for study use are labeled clearly as such, and their use is restricted to study infants or potential study infants. To enrich our chances of success, laptop, oximeter, and incubator will be locked together with a cable and key lock. The charge nurse will maintain a key for the cable lock in the event that the infant is transferred to another bed. An additional copy of the key will be kept in the narcotic cabinet for security purposes. Nurses will continue to record pulse oximetry on the vital sign sheets per the normal nursery practice. Values from the computer or oximeter may be recorded according to the practice in that nursery.
In generating and gathering the most reliable data possible with the technology available, it is important for the nurses caring for enrolled infants to understand completely the study protocol and the equipment being used. For this reason, in-service teaching will be conducted by an Ohmeda representative, the study neonatologist(s) and Study Center Coordinator(s) (SCC) to discuss the protocol prior to the project being instituted at any center. Inservice teaching on the use of the oximeter and laptop computer will include specific directions on the optimal placement and management of the probes.

The infant's oxygen should be adjusted to maintain the midpoint of the assigned oxygen treatment range. However, brief episodes of crying or movement result in only transient desaturation episodes and cannot be controlled. Therefore, attempts should not be made to adjust the oxygen for brief episodes that are anticipated to last for less than one minute. If relatively small changes in oxygen saturation do not suffice to achieve the desired goals, nurses should request assistance from the physicians to determine if other treatment parameters (such as ventilator settings) should be adjusted. In addition, an ongoing program of education about the study will be organized and carried out for the staff of each participating nursery by the study neonatologist and SCC.

7.3.2.4 Parents' instructions for home monitoring. In some cases the infant will be discharged to home before treatment completion has been reached. In this situation parents who agree to continue monitoring will be able to collect data while at home. The study will provide the oximeter and the laptop, and the SCC will instruct the family how to set up and use the equipment. Parents should be encouraged to maintain the midpoint of the assigned oxygen treatment range. In certain situations infants might receive oxygen at home. After receiving appropriate training, home oxygen use would be controlled by the parents, based upon assessment of pulse oximetry readings and the infant's condition. This is analogous to the nurses adjusting oxygen administration based upon pulse oximetry readings and clinical observation of the infant in the hospital setting. The parent will be instructed to notify the SCC and the infant's pediatrician of significant changes in saturation values or in the amount of oxygen required to maintain saturations in the assigned range.

The child will require weekly eye examinations, which must be arranged by the SCC. Such arrangements might include transportation. The infant will continue to require continuous monitoring in the home with the pulse oximeter and laptop until he or she reaches study endpoint.

Before study equipment is provided to parents, the SCC should initialize a blank diskette with the infant's STOP-ROP ID. Remove the current diskette and be sure it is correctly labeled. Place it in the infant's study file.
EXHIBIT 7-5

LAPTOP MONITOR SCREEN

Oximeter: SAT = 92

Patient name: Baby Girl
Date: 01/06/93
Time: 17:29:52

Program status: Collecting data until 22:49
Alarm status: Silenced

Current SaO2: 92
Avg of last 10 minute's SaO2: 91.5
Avg of last 60 minute's SaO2: 92.3

80 85 90 95 100
0 10 20 30 40+ % time: 20 mins

90 95 100
0 10 20 30 40+ % time: 4 hours

One hour saturation graph
Target is 89 - 94
Label a blank diskette with the Namecode, the STOP-ROP ID and the start date. To initialize the blank diskette turn on the laptop. The screen will ask you if you would like to continue the infant's session. Confirm that the STOP-ROP ID displayed on the screen is correct, put in the blank diskette and press the [Y] key. The laptop will then display the message: "This is not the infant's session disk, this disk is blank (no data on it.) Do you have the floppy disk for this infant's session?" Respond "No" by pressing the [N] key. The laptop will then copy from the hard disk onto the floppy diskette the infant's STOP-ROP ID and previous data. When the parents return for the next weekly examination the SCC will obtain from them the diskette containing the data collected at home and exchange it with the diskette from the infant's study file. When the parents come for each weekly eye examination they should bring the diskette and give it to the SCC. The diskette brought in by the parents will be exchanged with the diskette stored in the infant's study file. This exchanging of diskettes will continue until the infant reaches treatment completion. The last diskette to be collected from the parents should be labeled "FINAL" and sent to the Coordinating Center.

The Study Center Coordinator may check the compliance of a parent by requesting the parents to obtain the total cumulative compliance from the laptop. To view the total compliance from the screen, press the [TAB] key, then press the [C] key. The total compliance (TC) will appear in the extreme upper left corner of the screen. A total compliance of 65% would appear as "TC:65".

Compliance can also be checked by sending the diskette to the Coordinating Center. Label this diskette "interim". An interim compliance report will be produced at the Coordinating Center and distributed to the SCC. If the diskette is mailed to the Coordinating Center, then the SCC will either be required to initialize a second blank diskette before discharge or instruct the parents how to initialize the blank diskette.

7.4 BACKING UP SATURATION DATA AND TRANSMISSION

A 3.5 inch floppy data diskette can store up to 12 weeks of data. The data received by the laptop computer is comprised of the infant's saturation values which is sent every 40 seconds from the oximeter. These data could provide a rich source of ancillary studies.

7.5 OXYGEN MONITORING

Each infant will have oxygen use data collected at the time of entry and periodically until reaching the study endpoint and to three months corrected age. Please note that all standards for your Study Center in regard to oxygen monitoring should continue to be adhered to. If you normally assess pulse oximetry saturations with an occasional arterial blood gas, you should continue to do so. We do anticipate that arterial blood gases performed on infants in the supplemental treatment group will have PaO₂ values of 80-120 torr. Data to be collected for STOP-ROP include:
a) A "snapshot" of the infant's status before and after randomization: Oxygen concentration and mode of delivery will be recorded at the time of randomization. The same data will then be recorded on all infants 8, 16, and 24 hours after randomization in order to examine the changes needed to accommodate study assignment to supplemental or conventional oxygen.

b) The age at which the infant can maintain saturations of greater than 90% in room air will be recorded. The SCC will check the infant's saturations in room air at weekly intervals as follows:

   • After ensuring that the pulse oximeter is reading correctly, the oxygen concentration that the infant is breathing will be recorded.

   • If the infant is in room air, the saturation is then recorded.

   • If the infant is on oxygen and positive pressure ventilation (not CPAP), the presence of a ventilator and inspired oxygen level is recorded.

   • If the infant is receiving oxygen by CPAP, hood, or cannula, the oxygen will be turned down to room air, or by 10% decrements if the infant is in more than 34% oxygen. Please note: code 999 can be used if infant is too unstable to be placed in room air to determine his or her pulse oximetry saturation. Pulse oximetry will be watched continuously and the test continued for 20 minutes, provided that the saturation does not fall below 85%. If the saturation falls below 85% and continues to drop, the infant is immediately returned to the prior oxygen settings and the results of the test are recorded as "84%." If the saturation does not fall below 85%, record the lowest saturation obtained within the 20 minute period.

c) The last day that the infant received oxygen (even intermittently for procedures) will be recorded, unless it is an isolated event in the middle of a long period of days (more than seven) when no oxygen is needed. If the infant is still on oxygen at the three months corrected examination, this will also be recorded.
CHAPTER 8

OPHTHALMIC EXAMINATIONS
CHAPTER 8

OPHTHALMIC EXAMINATIONS

The procedures for conducting and recording the retinal examinations during the course of the STOP-ROP study are described in this chapter. Screening ophthalmology examinations are discussed and study required examinations at randomization and follow-up are described. STOP-ROP ophthalmic outcomes are defined as favorable or adverse. STOP-ROP retinal forms and instructions for completion by the study ophthalmologist are provided in Appendix 8A at the end of this chapter.

Retinal examinations for this study occur at the following time periods:

1. at baseline entry,

2. every week during treatment intervention until retina is fully vascularized or has sustained regression, or Threshold disease or beyond (stage 4 or 5) is documented in both eyes,

3. at 3 months corrected age (10-14 weeks post due date).

8.1

EXAMINATION TECHNIQUE

8.1.1 Dilating the Eyes

It is recommended that infants <36 weeks corrected age be kept Nothing by Mouth (NPO) 1 hour prior to instilling dilating drops, and that the next scheduled feeding not occur until one hour after the examination has been completed. For adequate dilatation, two applications of one drop of Cyclomydril (Cyclopentolate Hydrochloride 0.2% and Phenylephrine Hydrochloride 1%) should be instilled in each eye. Instillations should be 5 minutes apart, beginning one hour prior to the exam. For very darkly pigmented infants, a third instillation may be required. The examination of infants still in the NICU may be performed at the infant's bedside or on an examining table in a treatment room, but a NICU nurse or other qualified individual must be present throughout the examination to observe the infant's medical status. To preserve masking, the computer monitoring screen must be either turned off or covered so that the ophthalmologist remains masked to the study assignment.
8.1.2 Examination Procedure

The ophthalmologist employs the binocular indirect ophthalmoscope to examine the infant's fundus. Note that, when using a 28 diopter lens, visualization of the nasal retinal area may be subject to a prism effect from the crystalline lens, and that portions of the posterior Zone 2 will likely be included in the area under view. STOP-ROP uses the ICROP definition of Zone 1 only, and any Zone 2 area viewed should be ignored when determining the Zone 1 disease status. The standard examination technique is as follows, and proceeds in a logical order:

a) PLUS DISEASE: The posterior pole is first examined to determine the presence or absence of plus disease, as defined by a standard photograph. This must be done prior to scleral depression, since the hypotony following scleral depression tends to cause an increase in perfusion and false positive "plus disease" after the pressure is removed. Generally, the diagnosis of plus disease is based upon overall perception of the posterior pole vasculature. Each of the four corresponding quadrants of the fundus that are supplied by the four arteriovenous pairs of vessels branching from the central retinal artery and veins will be graded separately for the presence or absence of plus disease findings (Retinal Examination Form STOP 02). From these data STOP-ROP can determine the frequency of cases where plus disease occurs in the presence of normal appearing vessels in one or more of the four vascular branches.

An eye is considered to have plus disease if at least two of the four quadrants of the posterior pole vessels seen around the disc have dilatation and tortuosity that meets or exceeds the degree shown in the standard photographs.

Using a lid speculum and/or scleral depressor, the peripheral retina is examined next.

b) ZONE: Extremely immature eyes with vessels terminating in zone 1 are easily recognized. Zone 1 has a radius of twice the distance from the disc to the center of the macula (fovea) and is centered on the disc. The examiner will next visualize the ora serrata on the nasal side of the retina, that is, at 3:00 and 4:00 in the right eye, and 9:00 and 10:00 in the left eye. Ophthalmic findings in these two clock hours determine how the eye is classified and sectors are drawn and coded, as follows:

If vessels terminate well within one disk diameter of the ora serrata in both nasal clock hours, and there is either no nasal ROP or only fully regressed nasal ROP in these two clock hours, then the summary eye status is coded in zone 3 (codes 04 or 05) or fully vascularized (code 03). In any sector, all findings (i.e., any ROP or immature vessels, no matter how posterior) are drawn and coded in zone 3. Mature vessels are drawn and coded in zone 3.
If, in either of the two nasal clock hours, there is either active nasal ROP no matter how close it is to the ora serrata, or, in either of the two nasal clock hours, the anterior border of immature vascularization does not reach well within one disk diameter of the ora, then the eye is classified as a zone 2 eye (unless it is so posterior that it is a zone 1 eye), and immature vascularization and ROP are drawn and coded in every sector as zone 2 (or zone 1). However, sectors without active ROP that are completely vascularized to the ora serrata are drawn and coded on the Retinal Examination form (STOP 02) as completely vascularized in zone 3.

These definitions indicate that there cannot be active ROP in zone 3 in the nasal horizontal meridians. The conventions are summarized in the table below.

<table>
<thead>
<tr>
<th>Ophthalmic findings</th>
<th>How to code the summary eye status</th>
<th>How to draw and code the sectors</th>
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</thead>
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<td>In both nasal clock hours, vessels reach within 1 DD of the ora, and ROP is either absent or fully regressed</td>
<td>Zone 3 or Fully Vascularized</td>
<td>ROP, immature vessels, and mature vessels are in zone 3.</td>
</tr>
<tr>
<td>In at least one of the two nasal clock hours, there is either active ROP, or vessels do not reach within 1 DD of the ora.</td>
<td>Zone 2 or Zone 1</td>
<td>ROP and immature vessels are in zone 2 or 1. Mature vessels (within 1 DD of ora) without ROP are in zone 3.</td>
</tr>
</tbody>
</table>

c) **STAGE and EXTENT:** The stage of ROP, if present, is determined for each clock hour according to the International Classification of ROP [see Appendix H].

8.1.3 **Sterilization of Instruments**

Lid speculum and scleral depressors are each individually sterilized or disinfected before each use. Autoclaved individual instruments are preferred for study use. If disinfection is to be used, it should be with a wash in betadine or iodophor soap followed by a water rinse, a soak in 1:100 bleach solution for 10 minutes, and a rinse in sterile water. If your institutional infection control guidelines differ from this, follow your institutional infection control policy. The rim of the indirect lens should be wiped with an alcohol swab between infants. The examiner should wash hands with antiseptic soap between each infant or change gloves. Gloves must be worn if the examiner has any skin breaks on the
fingers and, in general, examiners should adhere to their hospital's policy regarding Universal Precautions during eye examination procedures.

8.2 EXAMINATION SCHEDULE AND RECORDING REQUIREMENTS

8.2.1 Screening Examination Schedule

While it is recognized that individual Study Center variations in screening of premature infants exist, for study purposes the following ophthalmology examination schedule supported by the Fetus and Newborn Committee of the American Academy of Pediatrics (44) is suggested for all STOP-ROP Study Centers. Prior to study initiation, each Study Center must submit the planned ophthalmology examination schedule to Study Headquarters for review.

- Examine all qualifying premature infants prior to discharge home and no later than 5-6 weeks after birth. Qualifying premature infants are defined by the following criteria:
  - less than 35 weeks of gestation at delivery and received oxygen for 6 or more hours
  - less than 1800 grams at delivery and received oxygen for 6 or more hours
  - less than 30 weeks of gestation at delivery, irrespective of oxygen exposure
  - less than 1300 grams at delivery, irrespective of oxygen exposure

- Repeat examinations for infants with at least one eye less than Prethreshold
  - Zone 3 immature vessels or ROP - every 2-3 weeks until mature/regressed
  - Zone 2 immature vessels or ROP - every two weeks if less than Prethreshold
  - Zone 1 immature vessels - every 1-2 weeks if less than Prethreshold

More severe ROP is Prethreshold and the infant is a candidate for the STOP-ROP study. The study schedule of weekly examinations will then be initiated.

8.2.2 Confirmation Examination

When an infant is determined during a screening examination to have met Prethreshold criteria defined in Chapter 6 of this manual (see also Exhibit 8-1), and is also eligible for STOP-ROP, the family is approached for consent. A second examination should be performed within 24 hours to confirm the findings of the initial exam. Of the two qualifying examinations required, at least one must be performed by a certified examiner. It is preferred that the second examination be performed by a certified examiner. If the first examination is performed by a certified examiner and a second certified examiner is not available to perform the second examination, the second examination may be performed by an uncertified examiner. If Prethreshold disease is confirmed, the certified examiner must complete the Retinal Examination form (STOP 02). If both examiners are certified, either
may complete the Retinal Examination form, provided that the interval between the two exams is no greater than 48 hours. If the interval exceeds 48 hours, the second examiner must complete the Retinal Examination form. Appendix 8A at the end of this Chapter provides a copy of this form and instructions for its completion. The Study Center Coordinator (SCC) will record the date and time of the two examinations, name and certification number (if applicable) of the examiner, and the diagnosis on the Baseline, Eligibility and Randomization form (STOP 01). If the examiners disagree before enrollment, they must discuss the discrepancies. If the diagnosis is not clear, the infant should not be enrolled, but appropriate follow-up should be arranged.

The SCC may help by taking notes during the procedure. The SCC will immediately examine the form (STOP 02) for completeness and clerical accuracy. One copy of the Retinal Examination form (STOP 02) and the Baseline, Eligibility and Randomization form (STOP 01) will be distributed to the infant's hospital record, one copy to the study file, and the original sent to the Coordinating Center. Black or blue pen should be used on all STOP-ROP forms.

If the parents consent to the study and the second examination confirms Prethreshold disease, the infant is randomized to a treatment arm, and at least weekly examinations continue to be performed by a certified ophthalmologist masked to the infant's study assignment.

The goal is to begin the assigned oxygen treatment within **24 hours** of making the initial diagnosis of Prethreshold ROP. If more than 24 hours pass from initial diagnosis of Prethreshold ROP to randomization, the infant may still be randomized, but will be designated a "Late Entrant" (see Section 6.6.1). If more than 48 hours have elapsed from the last exam by a certified ophthalmologist, a repeat eye examination by a certified ophthalmologist must document continued eligibility prior to randomization.
Exhibit 8-1

ROP Severity Definitions

**ROP SEVERITY**

<table>
<thead>
<tr>
<th></th>
<th>No stage</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4/5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plus disease</td>
<td>N/A</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Zone 1</td>
<td>&lt;P</td>
<td>P</td>
<td>T</td>
<td>P</td>
<td>T</td>
</tr>
<tr>
<td>Zone 2</td>
<td>&lt;P</td>
<td>&lt;P</td>
<td>&lt;P</td>
<td>&lt;P</td>
<td>P</td>
</tr>
<tr>
<td>Zone 3</td>
<td>&lt;P</td>
<td>&lt;P</td>
<td>&lt;P</td>
<td>&lt;P</td>
<td>&lt;P</td>
</tr>
</tbody>
</table>

Key:  
+  plus disease (at least 2 quadrants)  
3+  <5 contiguous and <8 composite clock hours of stage 3 with plus disease  
3++ ≥5 contiguous hours or ≥8 composite clock hours of stage 3 with vessels with plus disease  
<P  less than Prethreshold  
P  Prethreshold  
T  Threshold  
>T  Beyond Threshold

The following procedure should be used to determine the number of clock hours of stage 3 disease and whether a run of disease is contiguous. If the run has gaps (containing segments of ROP that are less than stage 3), this may alter the number of hours in the run, and also change a continuous run to a discontinuous run. The decision is made as follows: if a single gap is less than 1/2 clock hour, it may be ignored. If there is more than one gap, the examiner must estimate the total sum of all gaps within the run of ROP. If the sum is equal to or greater than 1/2 hour, it must be deducted from the run, and the run must be considered as discontinuous. If the sum is less than 1/2 hour, it can be ignored. If neither eye can be confirmed by the certified examiner to meet Prethreshold criteria, weekly examinations resume until enrollment criteria are met or the ROP regresses. If regression occurs without either eye reaching confirmed Prethreshold, the infant will then be documented in the register as having been excluded from the study, with the reason noted.
8.2.3 **Weekly Examinations**

At least weekly examinations will be performed for a minimum of two weeks, and until each of the infant's eyes reach either a FAVORABLE or ADVERSE outcome (see Section 8.3 for definitions). The infant should be examined by a certified ophthalmologist, masked to oxygen assignment. The ophthalmologist may use conventional eye examination form/chart notes, or the Retinal Examination form (STOP 02) to record weekly eye findings for clinical purposes. The current eye status must be provided to the SCC for recording on the Weekly Outcome form (STOP 03). The purpose is to determine if an eye has reached either an adverse or favorable endpoint or needs to continue follow-up. If either eye reaches a favorable or adverse outcome for the first time, a Retinal Examination form (STOP 02) must be completed and submitted to the Coordinating Center.

If a masked certified ophthalmologist is not available for an examination due to an emergency, the order of preference for examiners is as follows:

- unmasked, certified
- masked, uncertified
- unmasked, uncertified.

The ophthalmologist, SCC and neonatologist must decide at each examination who will communicate the results to the infant's parents. **THIS MAY BE DELEGATED, BUT CANNOT BE OMITTED.**

8.3 **STUDY OUTCOMES**

An ophthalmic study outcome will be defined as either a FAVORABLE or ADVERSE eye outcome or endpoint.

8.3.1 **FAVORABLE Eye Outcome**

A favorable eye outcome is defined as ROP regression by either of the following criteria, based on an examination by a certified ophthalmologist:

a) vessels are confirmed on 2 successive weekly examinations to have extended into zone 3, i.e., nasal vessels are within one disk diameter of the ora serrata nasally, but not temporally, or

b) mature vessels, defined as vessels that reach within one disk diameter of the ora serrata both nasally and temporally, are observed on a single examination.
8.3.2 **ADVERSE Eye Outcome**

An adverse eye outcome is defined as progression to Threshold or beyond using the following criteria:

a) ROP in zone 1, with plus disease, irrespective of stage of ROP  
b) ROP in zone 1, no plus disease, stage 3 ROP  
c) zone 2, with plus disease and stage 3 for 5 or more contiguous clock hours or 8 or more composite clock hours.

An adverse outcome is also defined as stage 4 or 5 and includes retinal fold, or partial or complete detachment (see Section 9.1). A true retinal detachment is defined as any unequivocal retinal detachment involving at least one 30 degree sector (full clock hour) of the vascularized retina and extending at least one disc diameter posterior to the ridge. Old circumferential cicatrices and tented vessels rising to the top of a ridge are not considered folds or detachments.

Threshold status and beyond (stage 4 or 5) must be confirmed by a second examination. Both of these examinations must be performed by a certified ophthalmologist. If the examiners disagree, they must either discuss the discrepancies and come to a consensus, or involve a third ophthalmologist to adjudicate. If the disagreement continues, a repeat exam should be scheduled as clinically indicated but in no event more than one week later.

8.3.3 **Procedure for Management and Follow-up of Infants with Adverse Eye Outcome**

If an eye progresses to Threshold disease, a masked certified ophthalmologist should complete a Retinal Examination form (STOP 02). The infant must be immediately referred to an appropriate ophthalmologist for possible cryotherapy or other treatment so that treatment can be completed within a targeted 72 hours. If the infant has been enrolled in the study for less than two weeks, weekly eye examinations and continuation of the assigned oxygen treatment are required regardless of the need for either cryotherapy or laser treatment.

In the rare event (e.g. unexpected absence or illness) a masked certified examiner is not available, an unmasked certified examiner may be used. If a certified examiner is not available, then a masked examiner, not certified for STOP-ROP, may be used. If the only examiner available is an unmasked, uncertified examiner and the examination cannot be rescheduled, the exam should still take place and the information recorded on the form. If an uncertified examiner performs the exam, code the two-digit STOP-ROP center number followed by 99 as the 4-digit certification number for the examiner on the form.
If one eye is at or beyond Threshold, while the fellow eye is not, some ophthalmologists will elect to treat both eyes simultaneously, to avoid delay, cause less stress, and spare the infant anesthesia. While the STOP-ROP study cannot dictate clinical practice, it is a Protocol Anomaly to treat both eyes when only one is at Threshold. Ophthalmologists confronted with such a scenario are asked to call the Study Chair, an ophthalmologist on the Executive Committee, or the Coordinating Center, to provide details of the ophthalmic findings prior to surgery. If the call is not possible because of the timing of surgery, a call to explain the circumstances must be made as soon as possible following surgery. In addition, a Protocol Anomaly form must be completed and submitted to document the case.

The SCC will request that another certified examiner confirm (or deny) the presence of Threshold disease and record this on the Retinal Examination form (STOP 02) along with the physician’s name and certification number. It is not necessary for both the initial examiner and the confirming examiner to complete Retinal Examination forms (STOP 02), but one of the certified examiners must complete the form. The confirming examination may be done by the surgeon if he or she is certified. If Threshold is confirmed in both eyes, and the infant has completed at least two weeks of assigned oxygen treatment, the infant may be taken off the study equipment. It is recommended that all retinal surgeons at a Study Center apply for certification.

If one eye remains at Prethreshold or less, and the other eye is at Threshold, both eyes will continue to be examined on a weekly basis even though the Threshold eye will have been treated, and the infant will remain on the assigned oxygen treatment until the non-Threshold retina is fully vascularized, shows sustained regression, or reaches Threshold.

8.3.4 Procedure for Management and Follow-up of Infants with Favorable Eye Outcome

If an eye is documented to have mature vessels or ROP is observed to be regressing in zone 3 on two successive weekly examinations, a certified ophthalmologist should complete a Retinal Examination form (STOP 02). If the infant has been enrolled in the study for less than two weeks, weekly eye examinations and continuation of the assigned oxygen treatment are required.

If one eye remains at prethreshold and the other eye has documented sustained regression, both eyes will continue to be examined on a weekly basis and the infant will remain on the assigned oxygen treatment until regression, fully vascularized or threshold or beyond occurs in the fellow eye.

In general, both eyes must be examined at weekly examinations and assigned oxygen treatment will continue until each eye has reached an endpoint (Threshold or beyond, vessels extended into Zone 3 for the second consecutive weekly examination, or
fully vascularized). There is one exception: no further examination of a fully vascularized eye is required, even if weekly examinations and assigned oxygen treatment are to continue because the fellow eye is not at endpoint.

8.4 PROCEDURE FOR MEDICALLY UNSTABLE INFANTS

If a randomized infant is deemed to be too medically unstable to undergo eye examinations, it is acceptable to reschedule examinations for the next possible date. If more than 10 days occur between examinations, a Protocol Anomaly form (STOP 06) is completed by the Study Center Coordinator and the reason for a missed visit documented. A neonatologist should document the reason why the examination was not performed in the infant's medical record.

8.5 THREE-MONTH FOLLOWUP EXAMINATION

At the time of the 3-month post due date examination, the infant will have both pediatric and ophthalmic follow-up examinations. The Three-Month Ophthalmic Outcome Examination form (STOP 04) will be completed by a study-certified ophthalmologist using the same ophthalmic examination techniques described in Section 8.1. [See Appendix 8A at the end of this chapter for a copy of the Three-Month Ophthalmic Outcome Examination form and instructions for completion.] Eye drops other than Cyclomydrol may be used according to the office practice of the examining STOP-ROP ophthalmologist.
APPENDIX 8A
Certified ophthalmologist: complete entire form at Baseline and when each eye first reaches an endpoint.

1. Visit number ........................................... (Code 00-Baseline, 01-Week 1, 02-Week 2, 88-Treatment Completion)

2. Date of Examination ...................................

3. EYE EXAMINATION SKETCH (to be completed by certified ophthalmologist)

Provide Findings by Clock Hours
[Mark highest stage in each sector]

(CODE: 0-No information 1-Demarcation line 2-Ridge 3-Extraret prolif 4-Retinal detach
5-Avascular 6-Incompl. vessel 7-Fully vascularized 8-Regressing 9-Regressed)

RIGHT EYE

ZONE 1 D plus disease

(all sectors)

ZONE 2

(all sectors)

ZONE 3

(all sectors)

STOP 02 VO2, 01/01/96
STOP-ROP
RETINAL EXAMINATION FORM [02]

STOP-ROP ID: ____________________  ____________________  ____________________  ____________________

<table>
<thead>
<tr>
<th>Center #</th>
<th>Hosp. Code</th>
<th>Patient #</th>
<th>RIGHT EYE</th>
<th>LEFT EYE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Stage 3 disease ........................................ (Code: 0-None, 1-Mild, 2-Moderate, 3-Severe)  ||

5. Hemorrhages (vitreous/retinal) ... (Code: 0-None, 1-Small, retina, 2-Large, retina, 3-Vitreous)  ||

6. Is active ROP present in Zone 1 or Zone 2? ................. (Code N-No Skip to 8, Y-Yes)  ||

7. STOP-ROP ophthalmic summary of active ROP
   a) Lowest zone with ROP ........................................ ||
   b) Worst stage in lowest zone with ROP  ........................................ ||
   c) Total clock hours of worst stage in lowest zone with ROP  ........................................ ||
   d) Longest number contiguous hours of worst stage in lowest zone with ROP  ........................................ ||
   e) Plus disease (at least two quadrants)  ........................................ (N-No, Y-Yes)  ||

8. Study Eye Status (use codes 01-99 below)  ........................................ ||

Adverse Eye Endpoint
01) * Threshold ROP *
02) * Beyond Threshold ROP *
   (retinal fold, detachment, or obscuring hemorrhage)

Favorable Eye Endpoint
03) * Fully Vascularized within 1 disc diameter of ora
   (may be quiescent old disease present) - No active ROP *
04) ** In zone 3 for the 2nd time in a row or more; immature vessels or less than Prethreshold ROP with/without regression **

Eye not yet at endpoint - continue to examine weekly
05) Zone 3 for the 1st time: immature vessels or less than Prethreshold ROP with/without regression
06) Zone 1 or 2: immature vessels or less than Prethreshold ROP with/without regression
07) Prethreshold present with or without some regressing ROP
08) Status post cryo or laser (no detachment)
99) Other (comment)

* If present for FIRST TIME, submit Retinal Examination form
** If in zone 3 for the SECOND TIME, submit Retinal Examination form

THRESHOLD VERIFICATION
Complete the first time answer to question 8 = 01 or 02 for an eye

Verification of Threshold disease or retinal fold or detachment was performed by: ____________________

Certification Number 9. ________________  
Name of Certified Ophthalmologist ____________________

Signature of Examining Certified Ophthalmologist ____________________

Certification Number 10. ________________

Signature of Study Center Coordinator ____________________

Certification Number 11. ________________

STOP 02 V02, 01/01/96
INSTRUCTIONS FOR STOP 02 FORM

RETINAL EXAMINATION

This form is completed at the following times during the STOP-ROP study:

- Prerandomization: Infant reaches Prethreshold status on 2 examinations, one of which was performed by a certified examiner.

  Note: Informed Consent must be obtained prior to completion of this form at the Baseline examination.

- Postrandomization: Endpoint for each eye after randomization (defined as the first time each eye reaches Threshold, retinal fold or detachment, or is fully vascularized, or second time regressing in zone 3)

The Study Center Coordinator and certified ophthalmologist are responsible for the completion and accuracy of information on this form. The Study Center Coordinator will complete the top portion of the form and submit it to the examining ophthalmologist. Following completion of the Retinal Examination form (STOP 02), the original should be submitted to the Coordinating Center and 2 copies maintained (1 for the infant's medical record if locally applicable, 1 for the infant's STOP-ROP study file).

GUIDELINES

The following guidelines are listed by question number and serve to supplement the instructions on the form and to assist you in understanding the interpretation of the findings and how to record them on these forms using study conventions. Not all questions are represented with guidelines. If a problem is encountered that the instructions or guidelines do not address, consult Chapter 8 of the Manual of Procedures or call the Coordinating Center or Study Headquarters. If a generic issue is identified, explanations will be provided for all centers.

3. Eye examination sketch - Provide a diagrammatic sketch of the ROP in each eye. These are not meant to be a "photograph", but are to be used to record the findings on paper and facilitate the coding by clock hour of the observed disease. Use the study conventions of coding the stages of active ROP according to the examples provided (see Figure 1).

   Plus disease - This question refers to the presence or absence of dilatation and tortuosity of the posterior pole vessels seen around the disc prior to initiating scleral depression. This subjective determination is made more objective by comparing the
findings to standard photographs provided. Although when present, it usually involves all four arteriovenous pairs of vessels, it is possible that fewer than four pairs of vessels will be involved and therefore the presence of plus disease in each quadrant will be recorded by circling $\bigoplus$ in each Zone 1 quadrant where it is present and circling $\bigotimes$ in each quadrant where it is not present.

An eye is considered to have plus disease if at least two of the four quadrants of the posterior pole vessels seen around the disc have dilatation and tortuosity that meets or exceeds the degree shown in the standard photographs.

**Zone** - Extremely immature eyes with vessels terminating in zone 1 are easily recognized. Zone 1 has a radius of twice the distance from the disc to the center of the macula (fovea) and is centered on the disc. The examiner will next visualize the ora serrata on the nasal side of the retina, that is, at 3:00 and 4:00 in the right eye, and 9:00 and 10:00 in the left eye. Ophthalmic findings in these two clock hours determine how the eye is classified and sectors are drawn and coded, as follows:

If vessels terminate well within one disk diameter of the ora serrata in both nasal clock hours, and there is either no nasal ROP or only fully regressed nasal ROP in these two clock hours, then the summary eye status is coded in zone 3 (codes 04 or 05) or fully vascularized (code 03). In any sector, all findings (i.e., any ROP or immature vessels, no matter how posterior) are drawn and coded in zone 3. Mature vessels are drawn and coded in zone 3.

If, in either of the two nasal clock hours, there is either active nasal ROP no matter how close it is to the ora serrata, or, in either of the two nasal clock hours, the anterior border of immature vascularization does not reach well within one disk diameter of the ora, then the eye is classified as a zone 2 eye (unless it is so posterior that it is a zone 1 eye), and immature vascularization and ROP are drawn and coded in every sector as zone 2 (or zone 1). However, sectors without active ROP that are completely vascularized to the ora serrata are drawn and coded on the Retinal Examination form (STOP 02) as completely vascularized in zone 3.

These definitions indicate that there cannot be active ROP in zone 3 in the nasal horizontal meridians. The conventions are summarized in the table below.
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<td>Zone 2 or Zone 1</td>
<td>ROP and immature vessels are in zone 2 or 1. Mature vessels (within 1 DD of ora) without ROP are in zone 3.</td>
</tr>
</tbody>
</table>

**Stage by clock hours** - Using the sketches to guide you, in every zone of each eye, complete the stage in individual clock hours according to the 0-9 key provided using the condition observed for each sector. If an entire zone contains a single stage, the corresponding number may be inserted in the space provided directly to the left or right of the zone diagram. Otherwise, when more than one stage or condition occur within a zone, the corresponding number must be placed in each sector of the zone diagram. If more than one stage or condition are present within a sector, record the most severe stage or condition. For example, if within a sector of a zone, there is evidence of regression but there is active ROP anterior to the regression, the stage of the active ROP should be recorded in the sector.

0 No information is used when you can not get information about the eye (eg, pupil would not dilate, view obscured)

1-3 Stage 1, 2 and 3 per ICROP definitions. If within a sector of a zone there is any active ROP, disregarding any regressed or regressing disease, code the most severe stage of active ROP present at the border of the vascularized and avascularized retina (the leading edge of vessel growth).

4 Retinal detachment may be of any degree, but must involve at least one 30 degree section (full clock hour) of the vascularized retina and extend at least one disc diameter posterior to the ridge.

5 Avascular means that the entire clock hour within that zone has no vessels (this will usually be zone 3)
Incomplete vessels is used when there is no ROP in the clock hour and there are vessels, but they have not crossed the entire zone. This is common in zone 2.

Fully vascularized means that the vessels have fully crossed the zone in that clock hour. If the nasal vessels are fully vascularized, any disease or even partially vascularized retina on the temporal side is recorded in zone 3 by study convention.

Regressing ROP is used (rather than "regressed" — see below) in a zone when there is evidence of ROP in the zone, with vessels extending anterior to it, but not attaining the zone boundary. In zone 3, the vessels are not within one disc diameter of the ora serrata.

The designation regressed ROP is used in any zone in which there is evidence of earlier ROP (cicatrix), but the vessels have now progressed to the next zone (for zones 1 or 2) or within one disc diameter of the ora serrata both nasally and temporally (for zone 3). Evidence of ROP (cicatrix) seen in zone 2 in an eye which now has vessels progressing into zone 3 is coded as regressed ROP in zone 2. There may be old cicatrix in the retina, but the active disease is gone. Fully regressed ROP in all 3 zones has complete vessels within one disc diameter of the ora serrata in both the nasal and temporal sides. If there is no evidence of old ROP in a fully vascularized eye, you may use code 7 or 9 if you are aware that ROP previously existed.

Examples of stage at clock hours:

A. All sectors were fully vascularized (7)

B. Sectors 11-6 contain a demarcation line while Sectors 7-10 are immature vessels without ROP. Numbers appear in each sector.
4. Stage 3 disease - Ophthalmologists should utilize their clinical experience and standard photographs located in Appendix I of the Manual of Procedures to describe as accurately as possible the severity of stage 3 in each eye. Record 0=none, 1=mild, 2=moderate, 3=severe.

5. Hemorrhages (vitreous/retina) - Small: one or more hemorrhages, with each having diameter less than 1 disc diameter at the narrower dimension and less than 2 disc diameters at the larger dimension. Large: any hemorrhage larger than these definitions is considered large. Vitreous hemorrhage is reserved for unequivocal bleeding in the vitreous. If several types of hemorrhage are present, code the most important: vitreous > large retinal > small retinal.

6. If the ROP is active and in zone 1 or 2, disregarding any regressed or regressing ROP, code Yes. If the ROP is not active or is in zone 3 (i.e. mature, cicatricial, regressed, regressing in all clock hours), code No and skip to Study Eye Status.

7. ICROP - For each eye: record the lowest zone of active ROP in any clock hour, worst active ROP stage in any clock hour, the number of clock hours of this worst stage, and the longest number of contiguous hours of the worst stage.

**NOTE:** when the total number of clock hours of worst stage is 01, for study convention purposes, the longest number of contiguous hours is also 01.

Record N or Y for plus disease. For STOP-ROP, the eye is considered to have plus disease if at least two of four quadrants have dilatation and tortuosity that meet or exceed the degree shown in the standard photographs.

8. Study Eye Status - Select the category which best describes the worst ophthalmic finding of each eye, and record that code. If other, specify findings on form in space provided.

Threshold ROP is defined by the following criteria:

a) zone 1 ROP, with plus disease, irrespective of stage of ROP as long as at least 1 clock hour of ROP is present
b) zone 1, no plus disease, stage 3 ROP
c) zone 2, with plus disease at the posterior pole and stage 3 for 5 or more contiguous clock hours or 8 or more composite clock hours.
WEEKLY OUTCOME FORM [03]

HOSPITAL ID NUMBER: ____________________

NAME CODE: ____________

1. Date of Examination ___________________________ M D Y

2. Status of infant at time of form completion
   1-Routine weekly examination prior to oxygen treatment completion
   2-Routine treatment completion: both eyes at endpoint, and at least 2 weeks post randomization
   3-Treatment prematurely terminated, but weekly follow-up continues
   4-Treatment prematurely terminated and weekly follow-up will not continue
   9-Other, please specify ________________________________

3. Follow-up visit number ___________________________
   (Code: 01-week 1, 02-week 2, 99-not weekly exam)

RESPIRATORY SUPPORT

4. Is the infant on oxygen? ____________________________ (N-No, Y-Yes)
   If NO, enter the last date the infant received oxygen and skip to e
   ____________________________ M D Y
   a) Mode of delivery
      1-Yes, but intermittently, skip to d
      2-Yes, on nasal cannula
      3-Yes, on hood
      4-Yes, on nasal CPAP [prongs]
      5-Yes, on ETT [vent or CPAP]
      9-Yes, other, specify ________________________________
   b) Oxygen concentration ____________________________ %
   c) If on cannula, enter cannula flow _____________________ L/min
   d) Pulse oximeter saturation on O₂ _______________________
   e) Pulse oximetry in room air recorded today

If infant is on oxygen with sat's ≥90%, discontinue for 20 minutes before recording saturation. If saturation drops below 85% return to ordered oxygen immediately, and record 84%.

Record 999 if the infant is too medically unstable to place in room air.

APNEA ASSESSMENT

5. a) Is the infant on an apnea monitor? ____________________________ (N-No, Y-Yes)
   b) Number of apnea and/or bradycardia episodes requiring stimulation recorded in past 24 hours ____________
   c) Is the infant on any methylxanthines? ____________________________ (N-No, Y-Yes)

PHARMACOLOGICAL SUPPORT

6. Is the infant on diuretics? ____________________________ (1-No
   2-Intermittently
   3-Daily)

STOP 03 V03, 01/01/96
STOP-ROP
WEEKLY OUTCOME FORM [03]

STOP-ROP ID: ____________________________
Center #  Hosp. Code  Patient #

7. Within the past week, has the infant received any steroids other than topical? ______
(1-No, 2-Yes, systemic for BPD, 3-Yes, systemic, not for BPD, 4-Yes, inhaled, 5-Unknown, infant enrolled in masked steroid clinical trial)

GROWTH ASSESSMENT

8. a) Current weight ____________________________ grams
b) Length _________________ cm
   • ________ Right eye
   • ________ Left eye
c) Head circumference _________________ cm

9. Study Eye Status (use codes 01-99 below) ____________________________

The ophthalmologist will use conventional eye examination form/chart notes to record the weekly eye findings for
clinical purposes and determine the current eye status as below. The purpose is to determine if an eye has reached
either the adverse or favorable endpoint, or needs to continue in follow-up. Confirm study eye status with the
ophthalmologist and record below. If answer is 1, 2, 3, or 4, Retinal Examination form must be submitted.

<table>
<thead>
<tr>
<th>Adverse Eye Endpoint</th>
<th>Favorable Eye Endpoint</th>
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</thead>
<tbody>
<tr>
<td>01) * Threshold ROP *</td>
<td>03) * Fully Vascularized within 1 disk diameter of ora</td>
</tr>
<tr>
<td>02) * Beyond Threshold ROP *</td>
<td>(may be quiescent old disease present) - No active ROP *</td>
</tr>
<tr>
<td>(retinal fold, detachment, hole or obscurring hemorrhage)</td>
<td>04) ** In zone 3 for the 2nd time in a row or more: immature vessels or less than Prethreshold ROP with/without regression **</td>
</tr>
</tbody>
</table>

Eye not yet at endpoint - continue to examine weekly
05) Zone 3 for the 1st time: immature vessels or less than Prethreshold ROP with/without regression
06) Zone 1 or 2: immature vessels or less than Prethreshold ROP with/without regression
07) Prethreshold present with or without some regressing ROP
08) Status post cryo or laser (not detached)
09) Other (comment)

* If present for FIRST TIME, submit STOP 02 form *
** If in zone 3 for the SECOND TIME, submit STOP 02 form **

10. Was ophthalmologist masked to treatment assignment at the time of the exam? ______
(N-No, Y-Yes)

Name of Examining Certified Ophthalmologist ____________________________

11. Certification Number ____________________________

12. Has a new episode of any of the following occurred since completion of the last STOP-ROP weekly
outcome form? ____________________________ (N-No, Y-Yes)

- Excessive Apnea and Bradycardia (number of episodes in a 24 hour period is triple the baseline and > 3)
- Documented hyperoxia (paO2 > 120 torr) while in the target range
- Documented hypoxia (paO2 < 45 torr) while in the target range
- Seizures (new onset)
- Necrotizing Enterocolitis
- Pneumonia/Sepsis with positive culture or requiring antibiotic treatment for more than five days
- Other serious events or events thought to be treatment-related

Reminder: If YES, complete an Adverse Experience (STOP 08) for each item.

Signature of Study Center Coordinator ____________________________
Date ____________________________

13. Certification Number ____________________________
INSTRUCTIONS FOR STOP 03 FORM

WEEKLY OUTCOME

This form is completed at the following times during the STOP-ROP study:

- Weekly, while on treatment or following, to document infant's progress
- Completion of oxygen treatment assignment (assigned oxygen treatment and study equipment at least for two weeks and until both eyes reach endpoints).
- Parents refuse further follow up (reminder: also complete the Protocol Anomaly form (STOP 06))

If a scheduled eye examination is cancelled and cannot be later performed within the visit time window, a Protocol Anomaly form (STOP 06) must be completed.

The Study Center Coordinator should attend the ophthalmic examination and obtain the study eye status from the certified ophthalmologist for recording on the Weekly Outcome form.

GUIDELINES

The following guidelines are listed by question number and serve to supplement the instructions on the form, not replace them. Not all questions are represented with guidelines. If a problem is encountered that the instructions or guidelines do not address, consult Chapter 9 of the Manual of Procedures or call the Coordinating Center.

1. For routine treatment completion (both eyes at endpoint and at least 2 weeks of assigned oxygen), the date of examination must be the date the infant is removed from assigned oxygen and study equipment.

2. Indicate the status of the newborn at the time of this exam, using the codes provided. Use codes (1) and (2) for routine exams. (1) indicates that other weekly exams will follow, while (2) indicates that no other weekly exams will follow.

Use codes (3) and (4) for non-routine situations, that is, situations in which treatment and/or follow-up are refused, or oxygen treatment is otherwise prematurely terminated. (3) indicates that other weekly exams will follow, for example, both eyes are not at endpoint and:
parents refuse further treatment but allow follow-up (Protocol Anomaly, form STOP 06, question 2a=Y).

follow-up is possible but oxygen treatment is prematurely terminated for other reasons (Protocol Anomaly, form STOP 06, question 2f=Y).

(4) indicates that no other weekly exams will follow, for example:

- Both eyes are now at endpoint but:
  - parents refused further treatment prior to both eyes reaching endpoints but allowed follow-up for at least the first two weeks (Protocol Anomaly, form STOP 06, question 2a=Y).
  - follow-up was possible but oxygen treatment was prematurely terminated and study equipment removed for other reasons (Protocol Anomaly, form STOP 06, question 2f=Y).

- Weekly follow-up is impossible because:
  - parents refuse (Protocol Anomaly question 2b=Y)
  - the infant will be permanently transferred to a non STOP-ROP facility (Protocol Anomaly question 2d=Y)

Note that, except for death and parental refusal of follow-up, the infant must be on assigned oxygen for at least 2 weeks before coding status 2 or 4.

3. The timing of follow-up visits begins from the day of randomization which is day 0. The window for a one week examination is ± 3 days [e.g., Week 1 examination can occur between Day 4 and Day 10; Week 2 examination can occur between Day 11 and Day 17]. If form is completed at times other than weekly exams, (e.g. parents refuse follow up, ophthalmologic endpoints attained in both eyes 2 days after a weekly exam) code 99.

4. Use of oxygen - If the infant is receiving oxygen, enter Y. If infant is not receiving oxygen, the last date that the infant received oxygen (even intermittently for procedures) will be recorded, unless it is an isolated event in the middle of a long period of days (>7) when no oxygen is needed.

4.a If infant is receiving oxygen intermittently, code 1; if continuously, select 2, 3, 4, or 5 to indicate mode of oxygen delivery. Code flooded isolette as 3- hood. Code masked CPAP as 4-nasal CPAP. If infant has a tracheostomy, select 9 and record trach, CPAP or vent. If the infant is receiving mixed respiratory support, code the highest level of support, e.g., infant is on
hood alternating with periods of nasal CPAP, code 4-nasal CPAP. For study purposes, the hierarchy is ETT > nasal CPAP > nasal cannula > hood.

4.b Oxygen concentration expressed as a %. When an infant is receiving oxygen by cannula, record the % oxygen the cannula is attached to, not the measurement of oxygen at the infant’s nostril area.

4.c L/min cannula flow - If infant is receiving 1/4 liter, record 0.25.

4.d Pulse oximeter saturation on O₂ - Indicate the median value recorded in the past 4 hours. Do not record recent acute changes in pulse oximeter saturation in this space (e.g. during eye exams or other procedures).

The laptop data collection program displays in the middle of the data collection screen a graph titled "% time: 4 hours". This graph uses horizontal bars to show the percents of time spent, over the past four hours, at various saturation values. The height of each bar (on the vertical axis) gives the saturation value, while the length of the bar (measured on the horizontal axis) gives the percent time spent at that saturation value. The bar corresponding to the median is identified by a dotted line drawn through it. Enter the saturation (vertical axis) value for this bar.

4.e Pulse oximetry in room air recorded today (within the past 24 hours) - If the infant is not receiving oxygen, record the median value in the past 4 hours. To obtain the median, follow the general directions given in 4.d above.

If the infant is receiving oxygen by CPAP, vent, hood, or cannula, the oxygen should be turned down to room air. The pulse oximeter will be watched continuously and the test in room air will be continued for 20 minutes, provided that the saturation does not fall below 85%. If the saturation falls below 85%, the infant is immediately returned to the prior oxygen setting and the results of the test are recorded as 84%. If the saturation does not fall below 85% in the 20 minutes, the lowest saturation obtained in that time period will be entered in the space provided.

5. Apnea assessment -

5.b Number of apnea/bradycardia episodes - Record the total number of apnea and/or bradycardia episodes which required stimulation or intervention in the past 24 hours. Example: if there were 2 apneic episodes requiring gentle stimulation, 1 combined apnea/bradycardic episode requiring bag
and mask ventilation, and 3 bradycardia episodes, but only one requiring stimulation, this would be recorded as $2+1+1=4$.

5.c Methylxanthines - Review the medical sheets for the past week in response to this question. Include drugs such as aminophylline, caffeine (Cafergot) and theophylline.

6. Diuretics - Drugs such as Lasix (furosemide), Diuril (chlorothiazide), Aldactone (spironolactone), and Edecrine (ethacrynic acid). Code 1-No, if the infant has not received a diuretic in the past week. Code 2-Intermittently, if the infant receives diuretics less often than once every other day, or if diuretics are ordered and have been given on a PRN basis in the past week (i.e. ordered PRN with blood transfusion). Code 3-Daily, if the infant receives diuretics once or more times per day, or every other day on a regular basis, or when the infant receives diuretics 5 days a week with two days off.

7. Review the medication sheets for the previous week. Systemic steroids are given for BPD if they are given for chronic lung disease; code 2 in this case. Laryngeal edema is not lung disease. If steroids are given for a few days around the time of extubation, the neonatologist must determine if the primary purpose is for the lungs (code 2), or for laryngeal edema (code 3).

If an infant has been on more than one category of steroid administration during the past week, record only the highest category; systemic for BPD > systemic non-BPD > inhaled > unknown.

Note: steroids administered by intraocular injection or nasal drops (e.g. Beclomethasone or Dexamethasone) are not considered systemic steroids; rather, they are to be considered topical.

8. Growth assessment - These measurements should be performed on the day of the follow-up visit or within 48 hours prior to follow-up visit.

8.a Weight - Record the infant’s weight in grams. If the infant is wearing a cast and is getting daily weights, the estimated dry weight of the casts should be calculated and subtracted from each applicable day’s weight.

A conversion chart is attached to these instructions, to use when a gram scale is unavailable.

8.b Length - Record the infant’s current length in centimeters, with one decimal place (e.g. 43.5). If the infant’s length cannot be measured (legs in bent cast, etc.), this data item will be missing for this examination, and should
be recorded as N/A. Attach a note to the data form explaining why the data item is missing.

8. c  Head circumference - To obtain, wrap the measuring tape around the head just above the brow and past the back of the head just above the base of the neck, at the maximum prominence of the occiput. Adjust the tape and remeasure two more times. Record the largest of the 3 measurements in centimeters with one decimal place (e.g. 32.5). If the infant has been diagnosed as having hydrocephalus and is receiving treatment for it (diamox or shunt or ventricular drainage), head circumference will not be analyzed and should be coded as N/A. Attach a note to the data form explaining why the data item is missing. If there is no ongoing treatment for diagnosed hydrocephalus, it is considered "arrested hydrocephalus" and the head circumference should be measured and recorded.

9. Study Eye Status - If scheduled retinal exam not performed, code N/A. Complete a Protocol Anomaly form, and attach explanatory note. In addition, skip questions # 10 and # 11. Otherwise, select the category which best describes the worst ophthalmic finding of each eye, and record that code. Choose the category that describes the worst sector in that eye. If other, specify findings on form in space provided.

Threshold ROP is defined by the following criteria:

a) zone 1, with plus disease, irrespective of stage of ROP as long as at least 1 clock hour of ROP is present
b) zone 1, no plus disease, stage 3 ROP
c) zone 2, with plus disease and stage 3 for 5 or more contiguous clock hours or 8 or more composite clock hours.

Prethreshold ROP is defined by the following criteria:

a) zone 1, any stage ROP less than Threshold.
b) zone 2, stage 2 ROP with plus disease, or
c) zone 2, stage 3 ROP any amount without plus, or if plus disease is present, <5 contiguous clock hours and <8 composite clock hours.
Fully vascularized is defined by the following criteria:

a) no active ROP, and  
b) vessels reach within one disc diameter of the ora serrata nasally and temporally.

When an eye has been previously reported as fully vascularized, while its fellow eye is not yet at endpoint, further examinations of the fully vascularized eye are unnecessary for the study protocol (until the 3-month follow-up), and eye status may be left blank. However, examinations may be performed, and status recorded, if the ophthalmologist so desires.

11. Provide certification number and name of certified ophthalmologist who performed retinal examination.

12. Report only adverse experiences that occur before the date you complete the weekly outcome form. When an adverse experience occurs prior to the first weekly examination, report it on the first weekly examination form. Events that happen on the date you complete the weekly outcome form should be reported on the next weekly outcome form. This will help us better track missing Adverse Experience reports.

Do not report adverse experiences that are continuations of previously unresolved adverse experiences. The Coordinating Center will periodically query you for the resolutions of ongoing adverse experiences.

13. Certification number and signature of Study Center Coordinator indicates form is completed and checked for accuracy.
THREE MONTH OPHTHALMIC OUTCOME EXAMINATION FORM [04]

(To be completed by a Certified Ophthalmologist)

STOP-ROP ID: __________________  __________________  __________________

   Center #  Hosp. Code  Patient #

HOSPITAL ID NUMBER: __________________

NAME CODE: __________________

1. Date of Examination ________________________________  M  D  Y

2. Is this visit outside the three-month examination window? [10-14 weeks post due date]
   (N-No, Y-Yes) ___
   If YES, code REASON:
   (1) Infant unable to maintain scheduled appointment due to illness or hospitalization,
   2) Parents unable to maintain scheduled appointment,
   3) Certified ophthalmologist not available,
   9) Other, specify ________________________________  ___

   RIGHT EYE  LEFT EYE

3. Vitreous opacity on or near visual axis
   a) Hemorrhage       (0-Absent, 1-Slight, 2-Moderate, 3-Extensive, 9-View obscured) ___  ___
   b) Membranes/organization (0-Absent, 1-Slight, 2-Moderate, 3-Extensive, 9-View obscured) ___  ___

4. Fundus
   a) Macular heterotopia       (0-Absent, 1-Questionable, 2-Present, 9-View obscured) ___  ___
   b) Optic nerve atrophy       (0-Absent, 1-Questionable, 2-Present, 9-View obscured) ___  ___
   c) Other                     (0-Absent, 1-Present, 9-View obscured) ___  ___

   If other is present in RIGHT EYE, specify: ________________________________

   If other is present in LEFT EYE, specify: ________________________________

STOP 04 V03, 01/01/96
STOP-ROP ID: ____________________________

RIGHT EYE  LEFT EYE

d) Retina

1) Fold ........................................ (0-Absent, 1-Present*, 9-View obscured) ___  ___
* If present, record clock hour orientation and extent.
Always indicate clock hour limit clockwise.

   a. Radial  ....................... (clock hours) ___ to ___  ___ to ___

   b. Zones involved  (0-Absent, 1-Present) ___ Z1 ___ Z2 ___ Z3 ___ Z1 ___ Z2 ___ Z3

   c. Circumferential ............ (clock hours) ___ to ___  ___ to ___

   d. Zones involved  (0-Absent, 1-Present) ___ Z1 ___ Z2 ___ Z3 ___ Z1 ___ Z2 ___ Z3

2) ROP cicatrix (old line) without fold  (0-Absent, 1-Present, 9-View obscured) ___  ___

3) Chorioretinal scars [document by drawings on pages 4 and 5 of this form]

   a. Cryo or laser  ..................... (0-Absent, 1-Present, 9-View obscured) ___  ___

   b. Other than cryo or laser ................ (0-Absent, 1-Present, 9-View obscured) ___  ___

4) Detachment or retinoschisis ....... (0-Absent, 1-Present, 9-View obscured) ___  ___

If detachment or retinoschisis, code location as follows: if some but not all hours detached, leave "all" blank and code 0 (absent), 1 (present), or 9 (View obscured) under each hour. If no (or all) hours detached, code 0 (or 1) under "all" and leave hours 1-12 blank.

RIGHT EYE

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<th>Zone</th>
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LEFT EYE

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<th>Zone</th>
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STOP 04 V03, 01/01/96
STOP-ROP
THREE MONTH OPHTHALMIC OUTCOME EXAMINATION [04]

STOP-ROP ID: ____________________________

5. Summary [Note: codes differ from CRYO-ROP form]
   a. View (1-Complete to ora serrata, 2-Out to vortex veins, 3-Only zone 1, 4-No fundal view)
      RIGHT EYE  LEFT EYE
   b. Most severe abnormality found for each eye
      01-Essentially normal
      02-Minor finding(s) (e.g. cicatrix, laser cryo scars) and/or abnormal angle of temporal vessels
      03-Macular ectopia
      04-Partial retinal detachment, retinoschisis, or fold in near periphery (sparring fovea)*
      05-Partial retinal detachment, schisis, or fold involving fovea*
      06-Cataract, retrolental membrane, or corneal opacity blocking view of macula (draw if possible)
      07-Total retinal detachment or schisis, or total retrolental membrane
      08-Status post vitrectomy
      09-Enucleation
      88-Unable to determine (e.g., corneal opacity unrelated to ROP, or miotic pupil making view impossible). Explain:
      RIGHT EYE: ___________________________________________
      LEFT EYE: ___________________________________________

      99-Other, specify:  RIGHT EYE: ___________________________________________
      LEFT EYE: ___________________________________________

   * Complete appropriate Fundus Sketches on pages 4 and 5 of this form

6. Are fundus drawings prepared?  (N-No, Y-Yes)  RIGHT EYE  LEFT EYE
   If partial detachment or chorioretinal scars, but no drawings, specify reasons:
   RIGHT EYE: ___________________________________________
   LEFT EYE: ___________________________________________

7. Are you masked to the assigned oxygen treatment of this infant?  (N-No, Y-Yes)  RIGHT EYE  LEFT EYE

8. Whether or not you think you know the treatment assignment, what is your best guess, or intuition?  (C = Conventional, S = Supplemental)  RIGHT EYE  LEFT EYE

9. Did infant have cryotherapy?  (N-No, Y-Yes)  RIGHT EYE  LEFT EYE
   If Yes, specify initial date
   M D Y

10. Did infant have argon or diode laser therapy?  (N-No, Y-Yes)  RIGHT EYE  LEFT EYE
    If Yes, specify: type of laser  (A = Argon, D = Diode)  RIGHT EYE  LEFT EYE
    initial date
    M D Y

11. Did infant have any other surgical treatment on the eyes?  (N-No, Y-Yes)  RIGHT EYE  LEFT EYE
    If YES, specify:
    RIGHT EYE: ___________________________________________
    DATE: M D Y
    LEFT EYE: ___________________________________________
    DATE: M D Y

12. Signature of Certified Ophthalmologist

13. Signature of Study Center Coordinator

STOP 04 V03, 01/01/96
14. DRAWINGS AT THREE MONTH EXAMINATION

COMPLETE IF PARTIAL DETACHMENT OR CHORIORETINAL SCAR PRESENT, OR AT THE DISCRETION OF THE OPHTHALMOLOGIST. Use Figure 1 of instructions for symbols. Black pen or dark colored pencils may be used.

RIGHT EYE

[Diagram of the right eye with annotations for clock hours and ora serrata]
15. DRAWINGS AT THREE MONTH EXAMINATION

COMPLETE IF PARTIAL DETACHMENT OR CHORIORETINAL SCAR PRESENT, OR AT THE DISCRETION OF THE OPHTHALMOLOGIST. Use Figure 1 of instructions for symbols. Black pen or dark colored pencils may be used.

LEFT EYE

CLOCK HOURS

ORA SERRATA

Sagittal View
INSTRUCTIONS FOR STOP 04 FORM

3-MONTH OPHTHALMIC OUTCOME

This form is used to assess ophthalmological study outcomes in the infant at 10-14 weeks post due date. Examinations which occur in this time frame are considered within the examination window. Example: an infant is born at 28 weeks gestation - 12 weeks post due date would be 24 weeks later (40 weeks is when the infant would have been born if he or she was full term; the 3-month examination is performed 10-14 weeks post due date: 12+12=24 weeks later). If it proves impossible to perform the examination within the window, it should be performed as close to the window as possible. The Study Certified Ophthalmologist is responsible for completion of the form. The Study Center Coordinator assures that the form is completed.

GUIDELINES

The following guidelines are listed by question number and serve to supplement the instructions on the form and to assist you in understanding the interpretation of the findings and how to record them on these forms using study conventions. Not all questions are represented with guidelines. If a problem is encountered that the instructions or guidelines do not address, consult Chapter 8 of the Manual of Procedures or call the Coordinating Center or Study Headquarters. If a generic issue is identified, explanations will be provided for all centers.

2. Examination window - The examination window is 10-14 weeks post due date. If the examination is outside the window, record the reason it was performed outside the window.

3. Vitreous opacity on or near visual axis - Consider findings within or overlying zone 1 to answer this question. Use 9-View obscured when there is a corneal or lens opacity blocking the view.

3.a Hemorrhages: slight range is 1 or 2 separate hemorrhages per eye, with each having neither a larger diameter than 1 disc diameter at the narrower dimension, nor 2 disc diameters at the larger dimension. Moderate range is 3-5 separate hemorrhages per eye, also with each having neither a larger diameter than 1 disc diameter at the narrower dimension, nor 2 disc diameters at the larger dimension. Any hemorrhages larger than these definitions either in size or quantity are considered extensive.
3. b Membranes/Organization: slight is considered to be anything the ophthalmologist feels is insignificant to visual acuity, moderate is potentially visually significant, and extensive means that this is obviously an obstacle to good visual acuity.

4. a) Macular heterotopia - Record 0 (absent) if the center of the fovea is positioned 2-3 disc diameters from the temporal disc margin and appears essentially undisturbed. If the macula is still 2-3 disc diameters from the disc margin but appears unequivocally dragged, record 1, (questionable). If the macula is 2 disc diameters or less from the temporal disc margin, or 3 or more disc diameters from the disc margin, record 2 (present). If the view of the fundus is obscured, then record 9 (view obscured).

b) Optic nerve - Record 2 if atrophy is unequivocally present. Record 1 (questionable) if you feel presence of atrophy is highly suspicious. Record 0 if only a slight question (please err on the side of under, not over-diagnosis). If the view of the fundus is obscured, then record 9 (view obscured).

c) Other - includes edema or 50% or greater cupping of the disc, or unequivocally larger cupping in one eye than the fellow eye. The question is left non-deductive in case there should be some other change you feel should be noted as a possible effect of ROP or cryotherapy (or unrelated but of potential prognostic significance). If the view of the fundus is obscured, then record 9 (view obscured).

d) 1) Retinal fold here may be located anywhere. For this item please err on the side of over-call, since something that looks like a fold may represent a significant disturbance. If you think "probably a fold" mark "present." The asterisk after "present" refers to the lines immediately following. If the view of the fundus is obscured, then record 9 (view obscured).

For the instructions under the asterisk, "clockwise" means that a fold from 11:00 to 2:00 represents 3 sectors, not 9, and should be recorded as

```
1 1 to 0 2
```

A fold from 2:00 to 11:00, however unlikely, represents 9 sectors and should be recorded as
2) At times there are residual membranes or cicatrix within the retina, but without a fold and with nothing near the visual axis. Record the observed presence or absence of such findings here. If the view of the fundus is obscured, then record 9 (view obscured).

3) If there are chorioretinal scars, determine if they are from cryotherapy or laser ablation for treating ROP and record accordingly. If they are not related to cryo or laser, use the "other than cryo or laser" choice. If the view of the fundus is obscured, then record 9 (view obscured).

4) Code 1 if there is an unequivocal retinal detachment involving at least one 30 degree section (full clock hour) of the vascularized retina and extending at least one disc diameter posterior to the ridge. Old circumferential cicatrices and tented vessels rising to the top of the ridge are not considered folds or detachments.

For zone 1, if detachment and/or retinoschisis is suspected, enter 1. For zones 2 and 3, if detachment and/or retinoschisis is questionable, record 0.

If the view of all zones is obscured, then record 9 (view obscured), and skip to question 4.

If the view is obscured in some zones, but not all zones, code 1 if detachment/retinoschisis is present in any of the zones viewed or code 0 if detachment/retinoschisis is not present in any of the zones viewed. Complete the individual zone coding indicating the detachment/retinoschisis status of each sector (0-absent, 1-present, 9-view obscured).

If detachment and/or retinoschisis is present and extends 360°, you should use the first column "all" for simplicity for each zone; otherwise, enter 1 for each detached clock hour. Clock hour involvement should be coded using the labels for each hour as illustrated below:
5. Summary - Code using only the listed numbers on the form. These are NOT identical to-summary diagnosis codes used in previous forms or CRYO ROP classification codes.

   a) View - use the appropriate choice that best describes the amount of view that was obtained in each eye.
      1. Complete to the ora means that the view was to the ora in effectively all clock hours.
      2. If the ora cannot be seen, use this code if a good view was obtained at least out to the vortex veins.
      3. If it is possible only to examine the posterior pole, effectively only zone 1, use this code.
      4. If there is no view, use code 4. In the summary diagnosis in part b), this will mean that the summary diagnosis will be 88 and you will be asked to write in the reason.

   b) Summary diagnosis -

      01 Essentially normal, or minimally abnormal. Minor variations are tolerated here, particularly when they don't relate to ROP. Visible cryo or laser scars should not be considered essentially normal.

      02 Abnormal angle of the temporal vessels, or even abnormal angle of the nasal vessels—although if the nasal vessels are abnormal it is more likely there is a fold or macular ectopia present, in which case you should use the higher codes below. Other minor findings could
include peripheral cicatrix, and cryo or laser scars if there are no other more severe findings present.

03 Macular (or fovea) ectopia or distortion without retinal detachment or fold.

04 Partial retinal detachment, schisis, or fold sparing the fovea (including partial retrolental tissue opacity incorporating the retina) NOTE: If this code is used, please prepare a fundus drawing.

05 Partial retinal detachment or schisis or fold involving the fovea. This includes partial retrolental tissue opacity incorporating retina (detachment) and obscuring view of the fovea. NOTE: If this code is used, please prepare a fundus drawing.

06 Cataract, retrolental membrane, or corneal opacity from ROP blocking the view of the macula (draw if possible). This code can also be used for other ROP related pathology that results in the same blockage of the visual axis. This is used when it can be seen that there is not complete retinal detachment (see 07).

07 Used when there has been complete retinal detachment or there is such a complete retrolental membrane that you can not determine the condition of the remaining retina.

08 Use if the eye has had vitreoretinal surgery for ROP -- if for another diagnosis, the 99 code for "other" should be used and an explanation provided.

09 Use if the eye has been enucleated for complications of ROP -- if for another diagnosis, the 99 code for "other" should be used and an explanation provided.

88 Avoid using "unable to determine" if at all possible. Try to best categorize the eye according to the choices given. If you must use code 88, be certain to explain the circumstances. You may attach an additional note if necessary.

99 If other, please specify as a write in. In the rare event that an eye is at Threshold or still in the active stages of ROP at this 3 month examination, use code 99 and specify.
6. Fundus drawings - If partial detachment or chorioretinal scars, fundus drawings are required. At the discretion of the ophthalmologist, these drawings may also be used to illustrate unusual or positive findings.

7. If you think you know the infant’s assigned oxygen, then you are not masked.

8. Whether or not you think you know the infant’s assigned oxygen, use your knowledge, best guess, or intuition in choosing the oxygen treatment assignment of the infant.

12. Signature and certification number of the ophthalmologist indicates form is completed and checked for accuracy.

13. Signature and certification number of the Study Center Coordinator indicates form is completed and checked for accuracy.
Fundus Drawings

Use the last two pages of the form for drawings if you feel there is a partial detachment or chorioretinal scar, or if there are other findings that should be recorded. Conventions for regressing and regressed ROP and cicatricial changes are shown in Figure 1. Color is optional.

In using the sagittal sections, show elevated or intravitreous lesions; if it should be necessary to show a cross section other than sagittal, cross out "sagittal" and indicate opposing clock hours of section selected.
FIGURE 1

CODE FOR CICATRICIAL ROP

- Single hatching = Blue = RD
- White = Red = Attached Retina
- G with arrow = Green = Vitreous Traction
- Y = Yellow = Exudate
- P = Pigment
- H = Blood

Remnant of ridge or demarcation line
Regression with vessels growing through ridge
Double cross-hatching-neovascularization

skipped area
Cryo scars
CHAPTER 9

DEFINITION OF OUTCOME MEASURES
CHAPTER 9

DEFINITION OF OUTCOME MEASURES

STOP-ROP is a multicenter randomized clinical trial designed to assess the clinical course, prognosis, and effects of the administration of conventional versus supplemental oxygen to infants with prethreshold retinopathy of prematurity. Study outcomes for STOP-ROP are defined in this chapter. The primary outcome measure is the development of Threshold ROP. Secondary outcomes include other ophthalmic findings (e.g. retinal detachment) and pediatric outcomes (e.g. growth measures); both are measured at various times during the study. All outcome measures are prospectively determined in order to test the efficacy and safety of the proposed treatment intervention. Follow-up will continue after the infant’s discharge to home.

A final study evaluation is planned at three months after the date at which the infant would have been full term (three months corrected gestational age) to determine the outcome of the ROP and the infant’s general health status as it may have been influenced by the oxygen management assignment under study protocol. The gestational age used to determine the timing of this examination will be the one recorded at the time of randomization.

9.1  OPTHALMOLOGICAL OUTCOMES

The treatment being tested in this trial is systemic in nature, affecting the entire infant. However, infants have asymmetric severity of ROP more than 20% of the time, and the outcome of each eye will be determined separately. The final analysis will seek differences in response according to severity of initial disease.

9.1.1  Prior to 3-Month Examination

Eye examinations will be performed at least weekly following randomization and will continue until each eye has experienced either an adverse or favorable outcome. For the purposes of analyses, infants who die prior to reaching either an adverse or a favorable outcome will be considered to have reached an adverse outcome. Imputation of outcomes will be considered for infants who are lost to follow-up prior to experiencing an event. The incidence of those exceptions is expected to be 7% or less.
9.1.1.1 **Adverse Eye Outcome - Progression**

An adverse outcome for an eye will be defined as progression of the infant's ROP to Threshold or beyond. Note: Definition of Threshold for Zone 1 eyes is different from that used in the CRYO-ROP study. In addition, the definition of plus disease is refined further for this study (see Section 8.1.2)

**Type I:**

For the purpose of this study, Threshold ROP is defined as:

a) Zone 1 with plus disease, stage 1, 2 or 3 ROP

b) Zone 1, no plus disease, stage 3 ROP

c) Zone 2, with plus disease and stage 3 for 5 or more contiguous clock hours or 8 or more composite clock hours.

When at least one eye progresses to Threshold, the infant is referred to a masked study-certified ophthalmologist for confirmation of progression, recording the eye examination findings, evaluating the infant for possible therapy, and for treating as clinically indicated. If a masked certified ophthalmologist is unavailable, refer to Section 6.7.2 of the Manual of Procedures to determine hierarchy of preference for ophthalmic examinations.

The assigned oxygen therapy will be continued for a minimum of two weeks after randomization. If both eyes progress to Threshold or beyond during that time, the assigned oxygen treatment will revert to routine management after the two weeks. If one eye remains less than Threshold, the infant will continue on the assigned treatment until retina is fully vascularized, or the ROP progresses to Threshold or beyond, or regresses to zone 3 as defined below. Therapy for Threshold ROP or beyond should not be delayed.

**Type II:**

"Beyond" Threshold is defined as:

a) any unequivocal retinal detachment (stage 4) involving at least one 30 degree sector (full clock hour) of the vascularized retina and extending at least one disc diameter posterior to the ridge.

b) any retinal fold. When located within 2 disc diameters of the ora serrata, a single fold must be larger than one disc diameter, and more than one fold must add up to more than one disc-diameter. Circumferential folds must be differentiated from vitreous condensation left over from previous active ROP. If in doubt, it is NOT a fold.

c) retinal hemorrhage in zone 1 that obstructs the view of the fovea or is considered to be obscuring a retinal hole, detachment, or fold.
9.1.1.2 **FAVORABLE Eye Outcome - Regression**

Since all study patients will have ROP in zone 1 or 2, regression will be defined for the purposes of this study as:

a) vessels which are fully vascularized: i.e., no active disease, growth of the vessels into zone 3, and the vessels reach within one disk diameter of the ora serrata nasally and temporally. The observation of full vascularization needs to be made only once to be considered a favorable outcome;

or

b) vessels are confirmed on 2 successive examinations to have extended into zone 3.

**Assigned oxygen treatment will continue for at least 2 weeks post-randomization, irrespective of the eye progression/regression.** Oxygen treatment assignment will continue beyond 2 weeks until BOTH eyes have met either regression or progression outcome criteria.

9.1.2 **At 3-Month Examination**

All randomized infants will be examined 10-14 weeks post due date. Examinations that occur in this time frame are considered to be within the examination window. If it proves impossible to perform the examination within the window, it should be performed as close to the window as possible.

**EXAMPLE:** An infant is born at 28 weeks gestation. 12 weeks post due date would be 24 weeks later. [40 weeks is when the infant would have been born if he or she was born at full term. Therefore the three-month exam is performed 10-14 weeks after the infant's original due date for delivery.]

The Three-Month Ophthalmic Outcome Examination (STOP 04) form must be completed at this visit.

**NOTE:** Rarely, an infant may not attain ophthalmic endpoints at the three-month corrected age examination. In this circumstance, three-month examinations should be completed on target and study equipment discontinued. The final diskette and study forms should be submitted to the Coordinating Center. Two weeks after receipt of three-month examination forms, the Coordinating Center will mail the Six Month Ophthalmic Outcome form (STOP 04A) to the Study Center Coordinator. When the infant reaches ophthalmic endpoints in both eyes, or six months corrected age, whichever is earlier, the examining ophthalmologist (certified preferred) should complete the Six Month Ophthalmic Outcome Form (STOP 04A).
9.1.2.1 \textbf{ADVERSE Eye Outcome}

An eye outcome will be determined for each eye separately and considered ADVERSE if:

\textbf{Type I}: the eye progressed to Threshold disease

\textbf{Type II}: The eye progressed beyond Threshold disease (retinal detachment, retinal fold, retinal hemorrhage). See Section 9.1.1.1

9.1.2.2 \textbf{FAVORABLE Eye Outcome}

Each eye that is not ADVERSE will be considered to be FAVORABLE.

9.2 \textbf{PEDIATRIC OUTCOMES}

Several aspects of the neonatal course might be expected to change in response to the assigned treatment, and broadly these are growth, ventilatory stability, chronic lung disease, neurological maturation, and length of hospital stay.

9.2.1 \textbf{Prior to 3-Month Examination}

9.2.1.1 \textbf{Growth}

Growth will be assessed by obtaining weight, length, and head circumference at weekly intervals beginning at enrollment and continuing until the oxygen treatment assignment ends. These measures will be repeated at the 3-month follow-up.

9.2.1.2 \textbf{Ventilatory Stability}

Apnea and bradycardia episodes are common features of prematurity and their frequency and severity are altered by oxygenation status. Nursery to nursery variability in definitions of apnea and bradycardia exist; therefore, for study purposes, we will compare only changes in the number of apneic and bradycardic episodes within infants. Two daily values will be recorded:

a) the number of apnea/bradycardia episodes requiring stimulation or resuscitation recorded by the nurses in a 24 hour period. These values will be recorded by the SCC on the infant's datasheet.

b) the number of desaturation episodes that occur on the pulse oximeter tracing will be recorded on the data diskette and reviewed by Study Headquarters.
In addition, the duration of use of ventilatory stimulants (caffeine, aminophylline, theophylline - all methylxanthines) will be recorded as an outcome variable. These data will be adjusted for post-conceptional age.

### 9.2.1.3 Chronic Lung Disease

Chronic lung disease may be improved by increased oxygenation, or conversely the lungs could suffer from the increased oxygen saturation on the basis of direct oxygen toxicity. Therefore, several aspects of these potential outcomes will be monitored:

- **a)** Survival
- **b)** Use of diuretics (post conceptional age when stopped)
- **c)** Special subset of infants with severe BPD.

### 9.2.1.4 Neurological Maturation

Formal neurodevelopmental assessment of these infants is complex, and the considerable expense for this endeavor cannot be justified for this study. However, the age at which the infant was able to take all feedings by nipple (three days in a row) will be recorded.

### 9.2.1.5 Hospitalization Stay

The duration of initial hospitalization will be recorded, which will sometimes require that the Study Center Coordinator (SCC) follow these infants by phone at referring hospitals. Duration will be defined as birth until first discharge to home. Should the infant require hospitalization after initial discharge to home, a Rehospitalization form (STOP 11) will be completed, indicating the date of admission and discharge.

### 9.2.2 At 3-Month Examination

All randomized infants will be examined 10-14 weeks post due date. Examinations that occur in this time frame are considered to be within the examination window. If it proves impossible to perform the examination within the window, it should be performed as close to the window as possible.

**EXAMPLE:** An infant is born at 28 weeks gestation. 12 weeks post due date would be 24 weeks later. [40 weeks is when the infant would have been born if he or she was born at full term. Therefore the three-month exam is performed 10-14 weeks after the infant's original due date for delivery.]
A Neonatal Outcome form (STOP 05) must be completed at this time. Outcome measure assessment procedures are defined in the Data Management Handbook.

9.2.2.1 Growth

At the 3-month examination, the SCC will weigh the infant, measure the infant's length and head circumference, and record these on the 3-Month Neonatal Outcome form (STOP 05). Growth from the time of enrollment into the study, adjusted for gestational age, will be compared between the two groups.

9.2.2.2 Chronic Lung Disease

If the infant is receiving oxygen and pulse saturations are <90%, the pulse saturation on oxygen will be recorded, in addition to the amount of oxygen the infant is receiving. Additional chronic lung disease risk factors will be recorded and include: parental smoking, atopy history, number of siblings in home. Those infants who qualified as severe lung injury at entry will have pulse oximetry saturation on oxygen and in room air (if saturations are \( \geq 90\% \)) measured.

The use of diuretics for all infants will be recorded as never received, currently receiving PRN, or previously received.

9.2.2.3 Interim Health Assessment

Interim health assessment will be determined by recording:
- Survival
- Rehospitalizations (if discharged home)
- Use of bronchodilators
- Use of diuretics
- Need for oxygen supplementation and/or ventilatory support

9.2.2.4 Developmental Screen

A modification of the Revised Denver Prescreening Developmental Questionnaire (STOP 09) (30) has been standardized against the Denver Developmental Screening Test and will be used to query the parents regarding infant developmental status [see STOP-ROP Data Management Handbook].
9.3 TERMINATION OF STUDY

9.3.1 Death

It is anticipated that some infants enrolled in this trial will expire during the study period. When this occurs, the attending neonatologist, following discussion with the STOP-ROP neonatologist, will complete a Death form (STOP 12) and submit it to the Coordinating Center. The date and primary cause of death will be indicated on this form. A copy of the infant’s discharge summary will also be submitted to the Coordinating Center when available. If the death is believed to be related to STOP-ROP treatment, an Adverse Experience form (STOP 08) must be completed.

If the parents are willing to give consent for autopsy, consent for examination of the eyes should also be sought. Several investigations are possible on these rare tissues, and Study Headquarters should be contacted regarding any new approaches. In lieu of alternative instructions, the eyes should be treated as follows:

- Removed as soon as parents are willing to permit
- Placed whole in 10% buffered formalin, at least 50 times volume
- After 24 hours of fixation, replace with fresh formalin
- After 48 hours of total fixation, embed the left eye in paraffin for sectioning
- NOTE: Avoid automated vacuum processors (do not use vacuum); sudden changes in pressures collapse newborn eyes.
- Place the right eye in 50% ethanol for storage.
- Send specimens by overnight delivery to:
  Nancy E. Wood, MPA
  Strong Children’s Research Center
  University of Rochester, Room 4-6245
  601 Elmwood Avenue
  Rochester, NY 14642
  Tel. 716/275-7746

9.3.2 Withdrawal of Consent

Families always retain the right to withdraw consent for the ongoing participation of an infant in any research project. A concerted effort should be made to determine why consent is being withdrawn and the problem addressed and solved if at all possible. However, if the parents are resolute, they should be asked if they would be willing to be contacted in the future for possible follow-up, even if they do not continue treatment. The results of this conversation should be documented in the infant’s medical records. Withdrawal from the study is reported immediately to the Coordinating Center on a Protocol Anomaly form (STOP06).
9.3.3 Unable to Monitor Oximetry

If for any reason it becomes impossible to monitor pulse oximetry, the SCC must immediately notify the Coordinating Center by telephone and identify the affected infant by the assigned study number, and indicate the reason for failure to monitor. A Protocol Anomaly form (STOP 06) must be completed and forwarded to the Coordinating Center. If the monitoring equipment has malfunctioned, arrangements will be made to provide the center with a replacement within 24 hours. All instances will be relayed to the Operations Committee for resolution. All infants randomized should remain under follow-up for all study endpoints regardless of the monitoring and oxygen administration status. Obvious exceptions to this procedure are infant's death or withdrawal of parental consent for further follow-up.
CHAPTER 10

MONITORING ADHERENCE TO PROTOCOL
CHAPTER 10

MONITORING ADHERENCE TO PROTOCOL

Several methods will be used initially to assure that each Study Center is fully trained to begin the study and then to monitor the ongoing progress of study accrual and data collection and management of individual infants.

10.1 CERTIFICATION PROCEDURES

Careful adherence to a common protocol at every level of patient management and data collection is essential in a multi-centered trial such as the STOP-ROP study. The quality of study data depends upon uniformity of observations and treatment techniques. The ultimate responsibility for seeing that each staff member is thoroughly familiar with the protocol and that care is taken to implement each aspect rests with the Principal Investigator in each unit. The Study Center Coordinator (SCC) will not only assist the Principal Investigator in identifying and resolving problems, but also serves as the key staff member at each Study Center in regard to protocol adherence.

10.1.1 Principal Investigators (PI)

The PI at each center is ultimately responsible for the performance of the study at that center. Each PI must be familiar with the Manual of Procedures and be willing to implement its provisions. The PI will attend the initial training session of the first Technical Group meeting and become certified as a participant according to specialty (neonatologist or ophthalmologist). The PI will have the responsibility to ensure that all members of the Study Center and the Center itself become certified in a timely fashion, and that appropriate procedures are arranged for informed consent. The SCC will report directly to the PI, but will work closely with all study neonatologists and ophthalmologists.

10.1.2 Neonatologists

Neonatologists who participate in the study will be encouraged to attend the initial Technical Group meeting as an introduction to the study, and at least one neonatologist from each center will be required to attend. For certification, each neonatologist must read the Manual of Procedures and submit an NIH Biographical Sketch and a letter of intent to participate to the Coordinating Center for forwarding to Study Headquarters. During the training session, the neonatologist must become familiar with the use of the Ohmeda 3740 pulse oximeter, oxytip neonatal probes, and associated laptop software.
The case studies distributed at the training session must be completed and submitted to the Coordinating Center for forwarding to the appropriate member of the Training and Certification Faculty for review. Following satisfactory completion, the neonatologist will then receive a unique study certification number to be used when completing study data forms.

10.1.3 Ophthalmologists

All participating ophthalmologists to be certified for this study must be fully trained and experienced in performing neonatal examinations and identifying ROP. Ophthalmologists requesting certification should be subspecialty trained in pediatric or retinal diseases, or have special training/experience in ROP. Residents are not eligible for certification. Fellows may be eligible, but require a special request from Study Headquarters. Each infant with potential for randomization requires an examination by two separate ophthamlic examiners. If the initial screening is performed by a noncertified ophthalmologist, then the subsequent confirming examination must be performed by a study-certified ophthalmologist. Before the center begins enrolling patients, at least two participating ophthalmologists must be certified, having demonstrated uniformity with the other investigators in the interpretation of the eligibility criteria.

Ophthalmologists previously certified to examine infants in Phase I of the CRYO-ROP study or other Study-Chair approved certification program have already demonstrated uniformity by performing dual examinations. These ophthalmologists need only read the Manual of Procedures and submit their NIH Biographical Sketch and a letter of intent to become certified for STOP-ROP to the Coordinating Center for forwarding to Study Headquarters, and complete case studies to obtain certification. Pediatric ophthalmologists certified by CRYO-ROP only in the long term follow up phase have not done dual exams on early ROP infants and will need to do so, in addition to completing case studies, to become certified.

For those ophthalmologists who wish to become certified and who did not participate in the CRYO-ROP trial, a training and certification course will be held after funding to individual centers is granted and prior to initiating any enrollment. This training and certification course will serve as the study's first Technical Group meeting. To gain certification, an ophthalmologist may attend this certification course, read the Manual of Procedures, and submit an NIH Biographical Sketch to the Coordinating Center for forwarding to Study Headquarters. In addition, case studies must be completed and submitted to the Coordinating Center. Following satisfactory completion, the ophthalmologist will receive a unique study certification number to be used when completing study data forms.

Examiners who are unable to attend the first Technical Group meeting for training or who entered the study at a later date, may become certified following demonstration of satisfactory agreement on masked dual examinations with a previously certified study examiner, and completion and submission of case studies. It is suggested that ophthalmologists examine five or more newborns prior to the actual certification process.
in order to maximize educational opportunity and minimize delays. These practice infants should be examined by each ophthalmologist separately and results recorded and compared after recording for agreement at the end of each examination. This should be done before examining the next practice infant to facilitate the educational process.

To obtain certification, the certified ophthalmologist and the candidate for certification must independently examine the eyes of five infants and complete STOP 02 form or their institution's ophthalmology form. Both physicians must examine the same infant within 24 hours. For the sake of the infants, examination within a single time frame is much preferred, since their eyes need not be dilated again. Of the five infants, at least three must have active ROP. It is best to compare the examination results after completion of the data forms for that infant, but prior to examination of the next infant, to learn from discrepancies. Note that the forms may not be changed after the comparisons are made. Eyes with mature vessels are ineligible for use in the certification examinations. These forms, the case studies, and an NIH Biographical Sketch will then be submitted to the Coordinating Center for forwarding to the Ophthalmologist Member of the Training Certification Faculty. Once certified, each ophthalmologist will be given a unique certification number to be used when completing study data forms.

10.1.4 Study Center Coordinators (SCC)

Each PI will designate a Study Center Coordinator who will be responsible for monitoring adherence to protocol at the Study Center. The SCC must be thoroughly familiar with study center activities and equipment. Each SCC will attend a special section of the initial Technical Group meeting for training and must become thoroughly familiar with all aspects of the protocol insofar as the operation of the Study Center is concerned. The SCC should maintain an up-to-date copy of the Manual of Procedures in a convenient place and encourage its use by all personnel. The SCC may be requested by the PI to assist in the process of obtaining informed consent. All problems related to protocol adherence should be brought promptly to the attention of the PI and the SCC, and both individuals should be notified of progress in solving problems related to protocol adherence.

10.1.5 Recertification Procedure

Study personnel must be re-certified annually. Re-certification is accomplished by attending the annual Technical Group meeting, in which a re-certification examination is given. Study personnel not attending the Technical Group meeting will be re-certified upon successful completion of the re-certification examination and submission of it to the Coordinating Center.
10.1.6 Study Centers

Until certification of a center is completed, the center cannot randomize an infant for oxygen therapy. A Study Center will be considered certified only after at least two ophthalmologists, a minimum of one neonatologist, and a SCC have completed certification and received certification numbers, and documentation of IRB approval has been received by Study Headquarters. Each Study Center must have a plan to address payment of costs associated with additional oxygen administration after the time the infant would have otherwise been discharged to home. In addition, selected NICU nurses must have been trained in the use of the monitoring equipment.

10.2 PROTOCOL-MONITORING TELEPHONE CALLS

The SCC will receive regularly scheduled telephone calls from the Protocol Monitor at the Coordinating Center. Initially, these calls are made monthly, gradually tapering off to be less frequent. The calls follow a structured agenda that is sent in advance to the SCC. The agenda includes the following:

- Staff changes and current or impending needs for training or certification
- Functioning and calibration of equipment
- Infant enrollment
- Satisfaction of parents with their infant’s participation in the study
- Satisfaction of staff with the working conditions
- Problems in meeting the requirements of the study
- Problems in completing data forms

These regularly scheduled telephone calls are designed to enhance positive communication. Rather than emphasizing errors made by the Study Center, which the Coordinating Center staff may do in other telephone calls, Protocol Monitoring Calls give each SCC the opportunity to report on the many ways in which the clinic is functioning properly and successfully.

The Protocol Monitor prepares for all Protocol Monitoring Calls by reviewing the data received from a Study Center, information about any errors made by the center, the certification status of new staff members, notes from previous calls, and recent correspondence from the Study Center.
The Protocol Monitor will maintain a log of telephone calls, correspondence, and site visits for each Study Center. The Protocol Monitoring Calls are not a substitute for other telephone calls that may be needed to resolve problems as they occur. Such calls should be made as often as needed.

10.3 SITE VISITS

During a long-term multicenter clinical trial, many anomalies may occur that can impair the validity of the data collected, and thereby the scientific integrity of the study. Among these are:

- Malfunctioning or improperly calibrated equipment
- Inadequately trained personnel performing study procedures
- Study personnel failing to perform procedures in the standard manner specified
- Study personnel forgetting to record observations on data forms

Periodic site visits to the Study Centers are an effective method to diminish any effect on the scientific integrity of the study and to achieve its goals.

Representatives of the Coordinating Center, Study Headquarters, and the Training and Certification Faculty will visit each Study Center in the first year, and as needed in subsequent years. The Executive Committee may request that additional study personnel participate in selected site visits.

The site visit will require a minimum of one working day. The goal of the visit will be to review all aspects of the Study Center operation. Site visits to certify ophthalmologists will be scheduled on the day that retinal examinations are performed at the Study Center. Retinal examinations will be observed on actual study infants whenever possible, or on infants with active ROP when study infants are unavailable. The site visit will be scheduled sufficiently in advance to facilitate Study Center staff participation. The Coordinating Center will distribute a copy of the site visit agenda to the Study Center PI and SCC prior to the actual visit. The site visit will include both formal and informal discussions to maximize communication regarding the overall objectives of the study.

The session will include discussion of the adequacy of current space and equipment and any staffing changes. Evaluation will be made of all the Study Center personnel regarding their time commitment to the study, their certification, their efforts to adhere to the protocol, and their concerns regarding study patients. Any problems that the Study Center personnel have with the Coordinating Center will be discussed at this time. The overview of the Study Center facilities will include an assessment of the adequacy of space for the SCC’s administrative work. Sample patient records will be reviewed as well as completion status of all necessary forms. A data audit will be performed by randomly selecting a minimum of 5 participants (if available) and comparing
the STOP-ROP master data file at the Coordinating Center with the clinical record and
STOP-ROP data forms. In addition, the existence of all enrolled infants will be verified.
At the conclusion of the site visit, the site visit team will meet with the SCC and PI to
discuss protocol adherence and problems detected during the site visit, and a summary
follow-up letter will be sent to the PI.

10.4 MONITORING OXYGEN SATURATION ADHERENCE

At the time of randomization, each infant will be placed on a pulse oximeter
connected to a laptop computer with the STOP-ROP saturation monitoring software
installed. Oximetry will be sampled once every 2 seconds and the data stored on disk
every 40 seconds. The summary distributions for the preceding 20 minutes and 4 hours,
and a one hour time trace, are displayed on the monitor screen. When the study is
completed for a particular infant, the data disk will be removed from the laptop and sent
to the Coordinating Center. These data will be used to monitor adherence with assigned
treatment.

10.5 EXPECTED ASSESSMENTS OF DATA QUALITY

The data forms will be completed and forwarded to the Coordinating Center on a
regular basis [see Appendix J for STOP-ROP Data Forms].

Data quality will be maintained through a variety of analyses that target anomalies,
delinquent data, and key-entry errors. A part of this process will be to analyze the
frequency of errors according to type to determine if certain types of errors are recurrent.
Modifications to the data forms will be made if the same types of errors occur frequently
among the Study Centers. If errors are localized within a Study Center, steps will be
taken to resolve the problems by providing additional training for Study Center staff
and/or modifying the forms.

10.5.1 Duplicate and error checks

Although the STOP-ROP identification system is designed to prohibit duplicates, a
check will be made periodically at the Coordinating Center to ensure that no undetected
duplicates remain. Following this check, another check of the database will examine the
individual fields and computed values within each record for illegal or conflicting entries.
Variables that are in error or inconsistent with other data will be compared to an anomaly
exception file.

The anomaly exception file is a means of documenting acceptable anomalies based
on the participant's STOP-ROP ID number and name code. The anomaly exception file
will be maintained by the Database Administrator at the Coordinating Center as a record
of resolved queries. It contains the STOP-ROP ID number, name code, and form and
question identifiers, as well as the reason for the exception and the date it was entered. A second date option is available if the exception has an expiration date.

10.5.2 Delinquent data

Delinquent forms will be identified and compared to an exception file. All missing forms will be grouped by site and a report file will be generated for distribution to the appropriate Study Centers. A missing form will continue to be requested either until the data for the form is submitted, or until an exception is granted and entered into the missing forms exception file.

Fields will also be checked for values which indicate that they are missing and were not recorded onto the form. Like the missing form and error/anomaly review, this program will identify the missing values by STOP-ROP ID number, name code, form, and variable. Reports which identify missing values are generated by site and mailed to the SCCs. Missing values will continue to be reported until completed or until an exception is granted.

10.5.3 Key entry errors

The accuracy of the data entered will be monitored by selecting a random sample of participant numbers and verifying the data entered into the system by comparing the original Study Center form with the information in the database. A report summarizing the results will be reviewed by the Coordinating Center, and a copy will be forwarded to the Operations Committee. Methods for improving the problems identified will be explored and modifications to the STOP-ROP forms will be considered.

10.5.4 Database integrity

The various components of the data processing will be audited periodically for accuracy and completeness.

A sample of data records will be selected for comparison with original clinic records. This audit will be performed by the Protocol Monitor during Protocol Review Visits. Errors will be resolved with the SCC where possible. The frequency of such errors will be tabulated and reported to the DSMC.
CHAPTER 11

STATISTICAL CONSIDERATIONS
CHAPTER 11

STATISTICAL CONSIDERATIONS

This chapter addresses the specific issues of sample size, patient availability, and planned analyses.

11.1 THE NUMBER SPECIFIC HYPOTHESIS

The unit of randomization in STOP-ROP is the infant, and the primary outcome is the development of Threshold disease. The primary objective of STOP-ROP is to test whether the administration of supplemental oxygen to infants with at least one eye at Prethreshold disease will result in a reduction by at least one third in the number of infants with one or both eyes progressing to Threshold ROP. Exhibit 11-1 provides data from the Natural History Cohort of the CRYO-ROP trial (25). Progression of Prethreshold ROP to Threshold ROP in at least one eye was observed in 245 out of 731 (33.5%) Prethreshold infants in this study. It is assumed that 80% of enrolled infants will have Prethreshold ROP in both eyes at the time of randomization, 10% will have Prethreshold disease in one eye and Threshold disease in the fellow eye, and 10% will have Prethreshold disease in one eye and less than Prethreshold disease in the fellow eye.

Specifically, STOP-ROP will be designed to test the null hypothesis,

\[ H_0: \pi_s \leq \pi_{oxy} \]

against the alternative,

\[ H_a: \pi_s > \pi_{oxy} \]

where \( \pi_s \) is the probability of an infant progressing to Threshold disease given conventional oxygen and \( \pi_{oxy} \) is the probability of an infant progressing to Threshold disease given supplemental oxygen therapy. Based on the CRYO-ROP results, \( \pi_s \) is assumed to be .30 and it is of interest to detect a 1/3 decrease in this rate in infants receiving supplemental oxygen therapy (\( \pi_{oxy} = .2 \)). Below we call the observed proportion of infants progressing to Threshold disease the "progression fraction."
## EXHIBIT 11-1

NUMBER AND PERCENT OF PATIENTS WITH VARIOUS CATEGORIES OF ROP BY SELECTED SUBGROUPS

<table>
<thead>
<tr>
<th>Subgrouping</th>
<th>Total Population</th>
<th>Prethreshold</th>
<th>Threshold</th>
<th>%P---&gt;Th</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>No. of Events</td>
<td>% of Events</td>
<td>No. of Events</td>
</tr>
<tr>
<td>Total</td>
<td>4099</td>
<td>731</td>
<td>17.8</td>
<td>245</td>
</tr>
<tr>
<td>Birth Weight (gm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;750</td>
<td>647</td>
<td>255</td>
<td>39.4</td>
<td>100</td>
</tr>
<tr>
<td>750-999</td>
<td>1590</td>
<td>341</td>
<td>21.4</td>
<td>108</td>
</tr>
<tr>
<td>1000-1250</td>
<td>1862</td>
<td>135</td>
<td>7.3</td>
<td>37</td>
</tr>
<tr>
<td>Gestational Age (wks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤27</td>
<td>1794</td>
<td>519</td>
<td>28.9</td>
<td>187</td>
</tr>
<tr>
<td>28-31</td>
<td>2027</td>
<td>204</td>
<td>10.1</td>
<td>55</td>
</tr>
<tr>
<td>≥32</td>
<td>278</td>
<td>8</td>
<td>2.9</td>
<td>3</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>2159</td>
<td>442</td>
<td>20.5</td>
<td>181</td>
</tr>
<tr>
<td>Black</td>
<td>1583</td>
<td>208</td>
<td>13.1</td>
<td>50</td>
</tr>
<tr>
<td>Other</td>
<td>357</td>
<td>81</td>
<td>22.7</td>
<td>34</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1970</td>
<td>367</td>
<td>18.6</td>
<td>118</td>
</tr>
<tr>
<td>Female</td>
<td>2129</td>
<td>364</td>
<td>17.1</td>
<td>129</td>
</tr>
<tr>
<td>Born in Hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inborn</td>
<td>3353</td>
<td>551</td>
<td>16.4</td>
<td>180</td>
</tr>
<tr>
<td>Outborn</td>
<td>746</td>
<td>180</td>
<td>24.1</td>
<td>65</td>
</tr>
<tr>
<td>Multiple Birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>3335</td>
<td>573</td>
<td>17.2</td>
<td>185</td>
</tr>
<tr>
<td>Other</td>
<td>764</td>
<td>158</td>
<td>20.7</td>
<td>60</td>
</tr>
</tbody>
</table>


2 Some infants classified as prethreshold are also classified as threshold if their ROP reached threshold.
11.2 REQUIRED SAMPLE SIZE

As oxygen therapy may be inferior, study termination and acceptance of $H_0$ may require less evidence than that which is required to prove benefit. We propose to implement an asymmetric group sequential method of analysis. Asymmetric test limits were introduced for sequential tests by DeMets and Ware (26) to allow early stopping when treatment is ineffective or harmful, while still allowing stringent early rejection of the null hypothesis in favor of treatment. Kim and DeMets (27) show how to adapt the error spending rate function approach to asymmetric boundaries. In contrast to the method of DeMets and Ware, this technique allows p-values to be calculated at any point in the trial, and as often as desired.

Using the software of Reboussin et al. (28) we constructed an upper-tail boundary with a total rejection probability of 0.025. The spending function for this boundary approximates an O'Brien-Fleming (29) boundary. This "spends" most of the rejection probability late in the trial. We also constructed a lower boundary with a total probability of 0.10. The spending function for this was constant, encouraging early rejection in the lower tail.

Suppose that, at time $t$, the numbers of individuals in the conventional and supplemental oxygen arms of the trial are $m_0$ and $m_1$, with observed progression fractions $\hat{P}_0$ and $\hat{P}_1$. Then the test statistic is:

$$Z_t = \frac{\hat{P}_0 - \hat{P}_1}{\sqrt{m_0^{-1} + m_1^{-1}}}$$

where $\sigma^2 = \overline{p}(1 - \overline{p})$, and $\overline{p} = (m_0\hat{P}_0 + m_1\hat{P}_1) / (m_0 + m_1)$ (45). Positive values correspond to successful supplemental oxygen treatment.

The method we will use permits inspection of interim results whenever and as often as desired. As a result, acceptance regions and power are not predictable without knowing inspection schedule and accrual rates. However, to give a feel for the method, Exhibit 11-2 shows acceptance regions for $Z_t$ when accrual is steady and equal, and there are 5 equally-spaced inspection times.

Exhibit 11-2 shows an upper O'Brien-Fleming type boundary, with exit probabilities as shown in the last column. These rise sharply as the trial proceeds, and sum to 0.025. Thus, most upper-tail rejection will occur late, and the final cumulative upper-tail rejection rate is 0.025. The lower tail "spends" equal amounts at each inspection time, so that the lower-tail exit probability is $0.10/5 = 0.02$ at each inspection time.
To better interpret these boundaries, Exhibit 11-3 shows them in terms of the progression fraction in the supplemental oxygen arm, $p_1$, when we assume that the standard progression probability is $p_0 = 0.30$, and the final sample size in each arm is 400. The equation for converting from $Z_c$ to $p_1$ is given in Appendix 11A.

Thus, under the assumptions of Exhibit 11-3, we will reject at the first inspection (with a sample of 80 in each arm) only if the progression fraction in the supplemental oxygen group is less than 0.0180 (positive result) or greater than 0.4575 (negative result).

Exhibits 11-4a and 11-4b show, as a function of the probabilities in both arms, the final sample sizes needed in each arm to attain powers of 0.8 and 0.9 respectively, for varied conventional and supplemental oxygen progression probabilities. Accrual is assumed steady and equal in each arm, and there are 5 equally-spaced inspection times. To get the final sample sizes, we used the software of Rezoussin et al to find a value $\Delta = E(Z_c)$ such that $Pr(\text{upper tail rejection}) = 1 - \beta$. Then, we set $N = 2\bar{p}(1-\bar{p})\left(\frac{\Delta}{p_0 - p_1}\right)^2$, where $\bar{p} = (p_0 + p_1)/2$.

The values of $\Delta$ are 2.84 and 3.28, for powers of 0.8 and 0.9, respectively. The trial is constructed in the hopes that it will end early. That is, the expected sample sizes will be smaller than the final sample sizes. The above values of $\Delta$ correspond to expected sample sizes that are only 80% and 74%, respectively, of the final sample sizes given in Exhibits 11-4a and 11-4b.

Exhibit 11-4b shows that, if the probabilities of progression in the conventional and supplemental oxygen groups are 0.3 and 0.2 respectively, then a final sample of 400 in each arm is enough to give a power of about 0.9. If there is a positive treatment effect, as discussed above, the trial is likely to end early, with only about 74% of the final sample size, or about 300 in each arm.
EXHIBIT 11-2

Acceptance regions for $z_e$ when accrual is steady and equal, and there are 5 equally-spaced inspection times.

<table>
<thead>
<tr>
<th></th>
<th>Lower 0.1</th>
<th>Upper 0.025</th>
<th>Upper exit probabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-2.0537</td>
<td>4.8679</td>
<td>.00000</td>
</tr>
<tr>
<td>2</td>
<td>-1.9141</td>
<td>3.3569</td>
<td>.00039</td>
</tr>
<tr>
<td>3</td>
<td>-1.7891</td>
<td>2.6803</td>
<td>.00341</td>
</tr>
<tr>
<td>4</td>
<td>-1.6797</td>
<td>2.2898</td>
<td>.00840</td>
</tr>
<tr>
<td>5</td>
<td>-1.5819</td>
<td>2.0310</td>
<td>.01279</td>
</tr>
</tbody>
</table>
EXHIBIT 11-3

Acceptance regions for $\hat{p}$, the progression fraction in the supplemental oxygen group, when the probability of conventional progression is 0.3, accrual is steady and equal in each arm, there are 5 equally-spaced inspection times, and the final sample size is 400 in each arm.

<table>
<thead>
<tr>
<th></th>
<th>Lower 0.10</th>
<th>Upper .025</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.4575</td>
<td>.0180</td>
</tr>
<tr>
<td>2</td>
<td>.4021</td>
<td>.1440</td>
</tr>
<tr>
<td>3</td>
<td>.3773</td>
<td>.1944</td>
</tr>
<tr>
<td>4</td>
<td>.3625</td>
<td>.2206</td>
</tr>
<tr>
<td>5</td>
<td>.3524</td>
<td>.2364</td>
</tr>
</tbody>
</table>
**EXHIBIT 11-4A**

Final sample sizes needed in each arm to attain power of 0.8 against the hypothesis that supplemental oxygen reduces the progression probability, for varied conventional and supplemental oxygen progression probabilities. Accrual is assumed steady and equal in each arm, and there are 5 equally-spaced inspection times.

\[ P_0, \text{ progression probability} \]

in conventional group

<table>
<thead>
<tr>
<th>( P_0 )</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>1.0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>77</td>
<td>37</td>
<td>207</td>
<td>65</td>
<td>305</td>
<td>370</td>
<td>24</td>
<td>41</td>
<td>97</td>
<td>102</td>
<td>402</td>
</tr>
<tr>
<td>0.2</td>
<td>8</td>
<td>11</td>
<td>16</td>
<td>25</td>
<td>45</td>
<td>97</td>
<td>370</td>
<td>24</td>
<td>41</td>
<td>97</td>
<td>102</td>
</tr>
<tr>
<td>0.3</td>
<td>5</td>
<td>6</td>
<td>8</td>
<td>11</td>
<td>15</td>
<td>21</td>
<td>34</td>
<td>65</td>
<td>207</td>
<td>37</td>
<td>77</td>
</tr>
<tr>
<td>0.4</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>8</td>
<td>9</td>
<td>12</td>
<td>16</td>
<td>23</td>
<td>37</td>
<td>77</td>
<td></td>
</tr>
</tbody>
</table>

\[ p_1, \text{ progression probability in supplemental oxygen group} \]

**EXHIBIT 11-4B**

Final sample sizes needed in each arm to attain power of 0.9 against the hypothesis that supplemental oxygen reduces the progression probability, for varied standard and supplemental oxygen progression probabilities. Accrual is assumed steady and equal in each arm, and there are 5 equally-spaced inspection times.

\[ P_0, \text{ progression probability} \]

in conventional group

<table>
<thead>
<tr>
<th>( P_0 )</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>1.0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>103</td>
<td>49</td>
<td>278</td>
<td>87</td>
<td>408</td>
<td>114</td>
<td>495</td>
<td>131</td>
<td>539</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>13</td>
<td>20</td>
<td>33</td>
<td>60</td>
<td>136</td>
<td>539</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td>10</td>
<td>15</td>
<td>22</td>
<td>34</td>
<td>60</td>
<td>131</td>
<td>495</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td>8</td>
<td>11</td>
<td>15</td>
<td>22</td>
<td>33</td>
<td>55</td>
<td>114</td>
<td>408</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>7</td>
<td>9</td>
<td>11</td>
<td>15</td>
<td>20</td>
<td>29</td>
<td>45</td>
<td>87</td>
<td>278</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td>5</td>
<td>7</td>
<td>8</td>
<td>10</td>
<td>13</td>
<td>16</td>
<td>22</td>
<td>31</td>
<td>49</td>
<td>103</td>
<td>0</td>
</tr>
<tr>
<td>0.7</td>
<td>.1</td>
<td>.2</td>
<td>.3</td>
<td>.4</td>
<td>.5</td>
<td>.6</td>
<td>.7</td>
<td>.8</td>
<td>.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ p_1, \text{ progression probability in supplemental oxygen group} \]
11.3 IDENTIFYING THE AVAILABLE POPULATION

The CRYO-ROP study has demonstrated that these infants are indeed a "captive audience" in the sense that they are obliged to remain hospitalized during the period that Prethreshold ROP normally develops. Therefore, all eligible infants will be identified through normal eye examination routines. Infants of any birth weight who have Prethreshold disease may enroll in STOP-ROP, provided parental consent is obtained. These infants may have been born at one of the participating hospitals or transferred in.

In CRYO-ROP, over 95% of parents consented to participate in the initial phase of the study. Since the hypothesis to be tested in STOP-ROP is more complex and potentially more risky, a 15% rate of non-consent is projected. However, during our pilot study, only 1 of 9 families refused.

11.4 PROJECTED TIME TABLE

Allowing for a 7% dropout rate before primary endpoint is reached, this study could require a total of 880 enrolled infants. However, if the treatment proves to be effective or deleterious, the trial will be stopped early, and fewer infants will be enrolled. The 23 CRYO-ROP centers enrolled 732 Prethreshold infants over 23 months. Assuming that 25±5 centers participate in STOP-ROP and that 80% of Prethreshold infants will be eligible for enrollment in STOP-ROP, recruitment will be complete in 3 years or less.

11.5 STRATIFICATION FOR RANDOMIZATION

Because the response to intervention may be correlated with the disease severity, infants will be stratified at the time of randomization. It is not anticipated that subgroup analysis will yield statistically significant results because of sample size limitations, but stratification will ensure an equitable distribution of severity between the two study groups. In order of descending severity:

**ONE EYE**

**FELLOW EYE**

<table>
<thead>
<tr>
<th>Stratum A</th>
<th>Stratum B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prethreshold ROP, any zone</td>
<td>Prethreshold ROP zone 2</td>
</tr>
<tr>
<td>Prethreshold ROP zone 1</td>
<td>Prethreshold ROP any zone</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Worse than Prethreshold (any zone)</td>
<td>Prethreshold ROP zone 2</td>
</tr>
<tr>
<td></td>
<td>Less than Prethreshold ROP (includes no ROP)</td>
</tr>
</tbody>
</table>
11.6 INTERIM ANALYSIS

At any particular time during the trial, an acceptance region constructed using the spending function method allows control of the final rejection rate but otherwise depends only upon current and previous inspection times. Thus, investigators may inspect when and as often as they like. Power may be affected, but not p-values. In general, the highest power is attained with a single inspection at the end of the trial, equivalent to a classical non-sequential test. The earlier and more frequent the inspections, the lower the power.

The primary variable of interest of each interim analysis will be the probability of progression to Threshold ROP in at least one eye among infants randomized. If there is insufficient evidence to stop the trial based on the opthalmologic endpoint of Threshold disease, enrollment will continue, providing there is no evidence of significant (p < .001) discrepancies in other measures of morbidity (lung function or neurologic deficits) or mortality. Note that these statistical tests can only be guidelines for trial termination. The statisticians at the Coordinating Center will work closely with the Data and Safety Monitoring Committee to evaluate the strength of the evidence for or against continuing the clinical trial. Supporting evidence will be sought from subgroup analyses and from the results of other studies. The results of all analyses will be reviewed by the Data and Safety Monitoring Committee, who will make a recommendation to terminate or proceed with the trial.

11.7 PROPOSED DATA ANALYSES

Both primary and secondary outcomes will be analyzed. Although the study is not designed with adequate power to compare treatment differences within strata, such treatment differences, should they exist, will be described.

11.7.1 Primary Outcome

The primary outcome of STOP-ROP is to compare the probability of Threshold ROP development in at least one eye in infants receiving supplemental oxygen to the probability of development in infants receiving conventional oxygen. The primary analysis will include all infants randomized, and infants will be analyzed according to the random assignment regardless of whether assigned treatment was subsequently administered (see Section 4.4). The normal approximation to the binomial will be used, and the test statistic at each interim analysis and the final analysis will be calculated as described in Section 11.2.
11.7.2 **Secondary Outcomes**

Several secondary outcomes are of interest, including both ophthalmologic and non-ophthalmologic processes. Specific measures are detailed below. Measurements will be made for each infant at several time points. We will modify the linear random effects approach of Lan & Zucker (46) to compare treatment and control groups with respect to outcome variables, which may be either continuous or discrete. Let $Y_{ig}$ denote the $n$-vector of responses of patient $i$ in treatment group $g$ ($=0$ or $1$), taken at time points following randomization $t_1 \ldots t_n$. Numbers of observations will likely differ between patients. (To simplify notation, we suppress the $ig$ subscript from the time points.) We suppose that:

$$ E(Y_{ig}) = X_{ig} \beta_{ig} $$

where $X_{ig}$ is an $n$ by $p$ design matrix, and $\beta_{ig}$ is a $p$-element vector of covariates. Both ordinary least squares and dichotomous regression models fit this framework, and provide asymptotically normal estimates $\hat{\beta}_{ig}$ and estimated variance matrices $\hat{V}(\beta_{ig})$. Assume that $\beta_{ig}$ is an observation from a distribution with mean $\beta_g$ and variance matrix $V_g$. Note that parametric values depend upon the treatment group.

To simplify the remainder of this discussion, concentrate upon $b_g$, a single element of $\beta_g$, with an associated variance $v_g$. (Multivariate extensions are possible, but of doubtful value.) A natural estimate for $b_g$ is:

$$ \hat{b}_g = \frac{\sum_i \hat{b}_{ig} \hat{v}_{ig}^{-1}}{\sum_i \hat{v}_{ig}^{-1}} $$

with estimated variance:

$$ v_g = \left( \sum_i \hat{v}_{ig}^{-1} \right)^{-1} $$

To test whether the parameter values differ between the treatment groups (0 and 1), we refer:

$$ \frac{\hat{b}_1 - \hat{b}_0}{\sqrt{v_1 + v_0}} $$

to a standard normal distribution.
Censoring may be related to the value of some outcome variables. For example, poorly growing infants may be weighed more often, particularly in the period between release from the hospital and the final 3-month checkup (while in the hospital, all infants will be weighed on a regular schedule). This is not likely to cause a severe problem, because, except for those who die or withdraw before the end of the study, data for all infants will span the same time-range, and, while in the hospital, will be observed at roughly the same time points. We expect deaths and withdrawals to be few. However, to investigate the effects of this phenomenon, we will compare analyses across strata defined by the amount of censoring.

**Ophthalmic.** A secondary ophthalmic endpoint is to compare the rate of infants developing threshold disease in both eyes among those treated with conventional oxygen versus those given supplemental oxygen. Based on the projected proportion of infants who will enter the trial with a) Threshold ROP in one eye, b) Prethreshold disease in both eyes, and c) less than Prethreshold disease in one eye, a rate of Threshold disease in both eyes of .25 (of all Prethreshold infants) is expected among infants given conventional oxygen. A sample size of 800 infants would provide 75% power to detect a decrease in the rate from .25 to .20 in infants treated with supplemental oxygen ($\alpha = .05$, one-sided). If the study is terminated at the second interim analysis due to a favorable outcome, 320 infants would provide over 90% power to detect a decrease in the rate from .25 to .15 among infants treated with supplemental oxygen ($\alpha = .05$, one-sided).

**Pulmonary status.** Chronic Lung Disease-related differences in ventilatory support, oxygen requirements, and diuretic therapy will be compared in infants with severe BPD. Oxygen saturations in room air will be measured for all infants at baseline, weekly during oxygen treatment, and at 3 months corrected age. The mean saturations for each treatment group will be compared. Age when diuretic therapy could be stopped, oxygen therapy could be stopped, and proportion of infants requiring bronchodilators and ventilators will be compared.

**Growth.** Differences in growth and development will be assessed using measures of head circumference, length, and weight. Measurements will include values at baseline, weekly during oxygen treatment, and at 3 months corrected gestational age.

**Cost Effectiveness.** Differences in cost-effectiveness will be measured by assigning costs to days hospitalized, days on oxygen, days of ventilator support, and level of nursing care required in various units during hospitalizations.

**Duration of hospitalization.** It is anticipated that infants with stable eye disease and without other complicating conditions will be discharged prior to the last study visit (3 months corrected age). It is of interest to determine if, as a group, infants receiving supplemental oxygen are discharged earlier than infants receiving conventional oxygen.
It is possible that the requirement for higher oxygen saturations among infants randomized to receive supplemental oxygen will cause some infants to remain hospitalized longer than normal due to the inability of the parents to reliably administer oxygen at home.

**Neurological development.** Several variables will be examined as surrogates for neurological development. They include the age nipple feeding was fully achieved and the results of the modified Revised Parental Denver Questionnaire (RPDQ)(30).

### 11.7.3 Operational Statistics

Analyses directed at monitoring the smooth and efficient operation of the study will identify problems and determine if modifications of study procedures are indicated. Some of the reports will include:

- Number of infants randomized by clinic, month, and cumulative total
- Number of missing forms by clinic
- Percentage of error-free data forms by clinic
- Number of dropouts by clinic and treatment group.
- Percentage of key entry errors

Infant characteristics will be analyzed within each treatment group in order to determine if randomization accomplished equal distribution of the following characteristics:

- Corrected gestational age
- Gender
- Race
- BPD status
- Baseline oxygen saturation in room air
APPENDIX 11A: Conversion from $Z_c$ to $\hat{p}_1$

Suppose that, at time $t$, the numbers of individuals in the standard and supplemental oxygen arms of the trial are $m_0$ and $m_1$, with observed proportions of progression $\hat{p}_0$ and $\hat{p}_1$. Then the test statistic is:

$$Z_c = \frac{\hat{p}_0 - \hat{p}_1}{\sqrt{\frac{1}{m_0} + \frac{1}{m_1}}}$$

where $\delta^2 = \delta (1 - \delta)$, and $\delta = \frac{(m_0 \hat{p}_0 + m_1 \hat{p}_1)}{(m_0 + m_1)}$ (Lan et al., 1993). This can be written $\delta^2 - c^2 \delta (1 - \delta) = 0$, where $c = Z_c \sqrt{\frac{1}{m_0} + \frac{1}{m_1}}$ and $\delta = \hat{p}_0 - \hat{p}_1$. Note that $\delta = \hat{p}_0 - \alpha \delta$, where $\alpha = m_1 / (m_0 + m_1)$. Then, $\delta^2 (\alpha^2 c^2 + 1) + \delta \alpha c^2 (1 - 2 \hat{p}_0) - c^2 \hat{p}_0 (1 - \hat{p}_0)$, from which:

$$\delta = \frac{c}{2 (\alpha^2 c^2 + 1)} \left[ \alpha C (2 \hat{p}_0 - 1) \pm \sqrt{\alpha^2 c^2 (1 - \hat{p}_0) (1 - \hat{p}_0)} \right]$$

Then, $\hat{p}_1 = \hat{p}_0 - \delta$. This will give two expressions for $\hat{p}_1$, one on either side of $\hat{p}_0$. We use the greater of the two if $Z_c$ is negative. Otherwise, we use the lesser.