Published in final edited form as:

Ophthalmic Epidemiol. 2017 February ; 24(1): 36–47. doi:10.1080/09286586.2016.1255765.

Postnatal Growth and Retinopathy of Prematurity Study: Rationale, Design, and Subject Characteristics

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Abstract

Purpose: Postnatal-growth-based predictive models demonstrate strong potential for improving the low specificity of retinopathy of prematurity (ROP) screening. Prior studies are limited by inadequate sample size. We sought to study a sufficiently large cohort of at-risk infants to enable development of a model with highly precise estimates of sensitivity for severe ROP.

Methods: The Postnatal Growth and ROP (G-ROP) Study was a multicenter retrospective cohort study of infants at 30 North American hospitals during 2006–2012. 65 G-ROP-certified abstractors submitted data to a secure, web-based database. Data included ROP examination findings, treatments, complications, daily weight measurements, daily oxygen supplementation, maternal/infant demographics, medical comorbidities, surgical events, and weekly nutrition. Data quality was monitored with system validation rules, data audits, and discrepancy algorithms.

Results: Of 11,261 screened infants, 8,334 were enrolled, and 2,927 had insufficient data due to transfer, discharge, or death. Of enrolled infants, 90% (7,483) had a known ROP outcome and were included in the study. Median birth weight was 1,070g (range 310–3,000g) and mean gestational age 28 weeks (range 22–35 weeks). Severe ROP (Early Treatment of Retinopathy type 1 or 2) developed in 931 infants (12.5%).

Conclusion: Successful incorporation of a predictive model into ROP screening requires confidence that it will capture cases of severe ROP. This dataset provides power to estimate sensitivity with half-confidence interval width of less than 0.5%, determined by the high number of severe ROP cases. The G-ROP Study represents a large, diverse cohort of at-risk infants undergoing ROP screening. It will facilitate evaluation of growth-based algorithms to improve efficiency of ROP screening.

Retinopathy of prematurity (ROP) is an important cause of blindness in children.[1, 2] If diagnosed in time, ROP can be effectively treated in most cases with laser retinal ablative

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None of the authors has any proprietary interests or conflicts of interest related to this submission.

The submission has not been published anywhere previously and is not simultaneously being considered for any other publication.

Presented in part at the 2016 Annual Meeting of the American Association for Pediatric Ophthalmology and Strabismus in Vancouver, British Columbia, Canada.

surgery[3–5], but detection involves subjecting at-risk infants to physically stressful, resource-intensive, and costly serial diagnostic eye examinations. Risk of ROP and the need for eye examinations are currently assessed using dichotomized cut off levels for birth weight (BW) and gestational age at birth (GA), but these simple criteria have poor specificity for identifying severe ROP. Less than 10% of infants examined require treatment in the United States[5–8], Canada[9], and United Kingdom[10, 11]. Nevertheless, because of the serious consequences of missing a case of ROP that might lead to blindness, the screening protocol must maintain high sensitivity, even at the cost of repeated examinations of children who never require treatment, many of whom do not develop retinopathy.

Insulin-like growth factor 1 (IGF-1) is a somatic growth factor that plays a permissive role in vascular endothelial growth factor (VEGF) mediated vessel growth during development.[12, 13] Loss of maternal IGF-1 and low endogenous IGF-1 production in premature infants lead to poor retinal vessel growth, retinal hypoxia, and the development of neovascular ROP.[13] Slow postnatal weight gain is a surrogate measure for low serum IGF-1 and has been found to be an excellent predictor for the subsequent development of severe ROP.[14–23] If a predictive model incorporating postnatal weight gain could be validated to more accurately predict ROP risk, changes to current screening guidelines could be proposed to reduce the number of infants requiring examinations or the number of examinations per infant. Multiple growth-based models have been developed, including WINROP, CHOP ROP, ROP Score, and CO-ROP.[16, 17, 19, 21, 23, 24] While these models have demonstrated high sensitivity for predicting severe ROP, the studies have been limited by sample sizes that are too small to provide precise estimates of sensitivity, a requirement to ensure that children needing treatment are not missed if a model were to be used clinically.[21, 25] Such precision is represented by the width of the confidence interval (CI) around the point estimate of sensitivity; this width is determined by the number of severe cases of ROP in the study cohort. To reduce the half width of the CI to <1% so that the lower boundary is above 99%, an adequately sized cohort must include hundreds of infants who develop severe ROP.

We report the design of the Postnatal Growth and ROP (G-ROP) Study, a large multicenter retrospective cohort study. The purpose was to study a sufficiently large cohort of at-risk infants to enable the development and evaluation of predictive models with very precise estimates of sensitivity for severe ROP.

MATERIALS and METHODS

The G-ROP Study was a National Institutes of Health, National Eye Institute supported, multicenter, retrospective cohort study of infants undergoing ROP screening at 30 hospitals in the US and Canada between 2006 and 2012 (Appendix A). The hospitals were selected to be geographically and racially diverse and to have a wide case-mix spectrum with regard to risk of ROP and complexity of care. The group includes hospitals at academic centers with ongoing multicenter study participation, tertiary referral center children's hospitals, and community-based hospitals with no clinical trial activity. Although not every hospital fit perfectly into one of these three categories, we estimate that there were 15 academic/university hospitals, 6 community hospitals, and 9 children's hospitals.

Institutional review board approval for the study was obtained at the study headquarters (The Children's Hospital of Philadelphia), the study data coordinating center (the University of Pennsylvania), and at all study hospitals.

Subjects

Subjects were infants born between January 1, 2006, and December 31, 2011, admitted to one of the G-ROP Study hospitals' neonatal intensive care units (NICUs). Infants were enrolled if they underwent ROP screening and had a known BW, known GA, and at least two postnatal weight measurements separated by 5 or more days and measured prior to 36 weeks postmenstrual age (PMA). Subjects were then excluded if, after ophthalmological data collection, they did not have a known ROP outcome. A known ROP outcome was defined for an infant as meeting at least one of the following conditions (A, B, or C):

A. Presence in *either* eye of Early Treatment of Retinopathy (ETROP) Study type 1 or type 2 ROP (any stage ROP in zone I, or stage 3 ROP in zone I or zone II, or plus disease)

B. Treatment performed in *either* eye (with laser, cryotherapy, anti-VEGF injection, or retinal detachment surgery)

C. Documentation of one or more of the following features in *each* eye: 1) mature retinal vasculature; 2) immature retinal vasculature in zone III without prior disease in zone I or II; 3) regressed stage 1 or 2 disease in zone II, or; 4) regressing stage 1 or 2 disease in zone II.

For the purpose of meeting these conditions, stage 3 ROP in zone 3 was categorized as type 1 ROP if there was plus disease, and as type 2 ROP if there was pre-plus or no plus disease.

Potential subjects were identified by reviewing hospital, neonatology, and ophthalmology records at each study center. Searches were completed for infants who met BW and GA ROP screening criteria in use during the study period, as well as for larger infants with a poor postnatal course who were examined at the request of the neonatologist. The BW criterion was <1,501g. The GA criterion was ≤32 weeks 0 days, because, although the recommended criterion during the study period was 30 weeks[26, 27], many hospitals had used 32 weeks.

Data collection

Infant demographic, medical, and ophthalmological data were abstracted retrospectively from written and electronic inpatient and outpatient medical records at each of the study centers. Data were collected by 65 certified data collectors and entered into a web-based database, which was designed with Oracle Clinical (Oracle Corporation, Redwood Shores CA, USA) and managed by the G-ROP Study data coordinating center (DCC) at the University of Pennsylvania in Philadelphia, PA. The data collector certification process included close review of the study protocol, manual of procedures, and data collection forms, completion of a webinar training session, mock data entry into a test database, and a written knowledge assessment test.

Ophthalmological data—Ophthalmological data were collected for all examinations until retinal vascular maturity or disease regression. Examinations were completed by fellowship-trained pediatric ophthalmologists or retinal specialists with ROP expertise, using International Classification of ROP (ICROP) terms.[28] The following information was collected for each eye at each examination: Highest stage of ROP (immature, stages 1 through 5, regressing, regressed, or mature vasculature); lowest zone of ROP (I, II, or III); presence of pre-plus or plus disease; and type and date of all treatments, including laser retinal photocoagulation, cryotherapy, retinal detachment surgery (eg, scleral buckle or vitrectomy), and intravitreal injection of an anti-VEGF agent, with name and dose of agent used. Documentation of other abnormalities, such as cataract, glaucoma, and retinal hemorrhage, was recorded. For infants who had received ROP treatment, additional data were collected up to 15 months of age on short-term and long-term findings and complications, including corneal abrasion or scar, hyphema, cataract, glaucoma, infection, macular ectopia, and retinal detachment or fold.

With regard to the reliability of retrospective ROP data, a hierarchy was established for the source of ROP data, from most to least preferred; ophthalmology consultation note, ophthalmology procedure note for ROP treatment, weekly ophthalmology ROP rounding sheets, and ophthalmology clinical database of ROP examination results. NICU progress, transfer, or admission notes were the least preferred source and were acceptable only as a source of ROP treatment type and date; NICU notes were not acceptable as source data for ROP stage, zone, or presence of plus disease from a ROP examination.

Medical data—Data were collected on factors that may be used as predictors in a model because of an association with ROP or postnatal growth. First, draft case report forms were evaluated in a feasibility study conducted at the study hospitals to determine which predictors were consistently documented and feasible to collect retrospectively. Variables that were clearly charted and did not need to be inferred were retained, such as BW, GA, and postnatal weight measurements. Variables that were frequently missing, recorded using ambiguous terminology, or not measured in a consistent manner were excluded. For example, postnatal head circumference and length measurements were collected irregularly across sites, were known to have greater measurement variability, and did not appear necessary for ROP prediction, because published models had successfully used weight gain alone as a measure of growth.[21] In addition, variables that were found to be very time consuming to abstract and unlikely to contribute significantly to ROP risk were also excluded, such as most medications. A description of the medical data collected follows below.

Infant BW in grams was abstracted from the labor and delivery record if available, or, if unavailable or noted to be inaccurate by the attending neonatologist, from the weight on admission to the birth hospital NICU. GA at birth was recorded as the best obstetric estimate, which was based on last menstrual period, obstetric exam, and prenatal ultrasound. This estimate was abstracted preferentially from the delivery note of the maternal chart or if necessary from the NICU chart. If the obstetric estimate was unavailable, the neonatology attending's estimate, as based on physical criteria and neurological examination, was abstracted from the NICU admission note. Postnatal weight measurements were collected

from nursing flow sheets from birth through 40 weeks PMA. Weights were typically measured every 1 or 2 days with the standard equipment in use at each site, reflecting the expected variations in practice that would be encountered should a weight gain ROP algorithm be used clinically.

High blood oxygen levels may cause VEGF inhibition, poor retinal vessel development, and damage to the developing retinal vasculature, resulting in subsequent retinal hypoxia and neovascular ROP.[29] Therefore, the administration of supplemental oxygen at any point during the day on each day for the first 6 weeks of life and at 36 weeks PMA was abstracted from nursing and respiratory flow sheets. Supplementation was defined as any administration of oxygen above 21% regardless of ventilatory support, delivery method, delivery flow rate, or duration of delivery on that date. This relatively crude proxy measure of oxygenation and respiratory status was concluded to be simple and reliably collected retrospectively. More complex or detailed measures of respiratory support or blood oxygen saturation levels were not recorded in a sufficiently consistent manner in the medical record to justify the added effort of collecting such data.

Maternal data collected included age, race, ethnicity, gravity, prenatal care, mode of delivery, multiple gestation birth, gestational diabetes, chorioamnionitis, and administration of full or partial course of prenatal corticosteroids. Infant birth data were also collected, including sex, head circumference and length, Apgar scores, and resuscitation efforts in the delivery room (supplemental oxygen, positive airway pressure, intubation, chest compression, and epinephrine).

Postnatal medical events data were collected through 36 weeks PMA. These data included grade III or IV intraventricular hemorrhage, periventricular leukomalacia, hydrocephalus, surgical treatment for hydrocephalus, surgical treatment for necrotizing enterocolitis, patent ductus arteriosus (PDA), PDA treatment with medication or surgery, all surgical events requiring general anesthesia, and all episodes of culture-positive sepsis or cerebrospinal fluid infection. Chromosomal and syndromic diagnoses were also abstracted. Weekly nutritional status was collected, including parenteral nutrition, enteral feeding, maternal breast milk, donor breast milk, and fortified feeds, as were vitamin supplementation with vitamin A, vitamin E, and multivitamins. Serum platelet levels were abstracted from laboratory reports through 40 weeks PMA, because thrombocytopenia has been associated with ROP.[30]

Data quality

Data quality was monitored through database validation rules, data audits, and discrepancy algorithms. All flagged potential errors were resolved, either immediately at the time of data entry or in response to DCC-generated data queries to the study centers, to which the centers responded with documentation supporting the entered data or correction of the error.

Validation rules at the time of data entry flagged potential errors; examples included range checks for single numerical values (eg, low or high BW) and serial values (eg, excessive daily weight gain or loss), flags for asymmetric interocular findings, and date checks (eg, comparisons between events and date of birth). Data audits were performed for each data collector, in which database information was compared to redacted source medical records

documents supplied to the DCC by study centers. Excessive error rates were remediated with additional data abstractor training, testing, and repeat audits.

Discrepancy check algorithms were developed to identify potential outlier, illogical, or erroneous values for daily weights and ROP diagnoses. All flagged values were investigated. For weight measurements, of which there were nearly 500,000 values, all daily gains or losses greater than 250g were reviewed by checking the preceding, day of, and subsequent days' values. For ROP data, numerous queries were used to identify erroneous data (Appendix B). For example, ROP follows a time course closely tied to developmental age (PMA) not chronological age. Therefore, occurrences of a specific ROP stage, zone, plus disease, treatment, or severe ROP, before or after expected PMA time points were investigated by reviewing source data at the centers, and either confirmed or corrected. Other unexpected sequences were flagged and investigated, such as an exam completed for an eye after diagnosis of mature vasculature in that eye, or regressing ROP in an eye that was not preceded by a stage of ROP. Similarly, ROP is typically a symmetric disease. Therefore, any 2-stage or greater difference between eyes was flagged. Finally, potential errors related to ROP treatment were flagged, such as treatment performed in an eye not meeting type 1 ROP criteria or type 1 ROP diagnosis without treatment.

Statistical analysis

Model development—Multiple modeling approaches have been described and will be assessed using the dataset, with the overall goal of developing a highly sensitive and specific model, which is easy to apply clinically. We will start with the approach used for the PINT ROP and CHOP ROP models[14, 31], which consist of a logistic regression equation that is calculated repeatedly on a weekly basis to predict the risk of developing ETROP type 1 or 2 ROP based on BW, GA, and daily weight gain rate over the prior week. If the predicted risk of ROP is greater than a cut point level, exams are indicated. We will consider other predictors as well if necessary, such as comorbidities of prematurity (sepsis, necrotizing enterocolitis, etc), days of oxygen supplementation, and nutritional status. However, in the development of the PINT ROP model, other predictors were considered, but they were no longer significant when weight gain was in the model, presumably because their associations with ROP are mediated through an effect on serum IGF-1. For example, sepsis lowers serum IGF-1, which inhibits retinal vessel growth. Low serum IGF-1 lies in the causal pathway connecting sepsis with ROP. Therefore, one does not need to consider sepsis in the prediction of ROP if one considers serum IGF-1. Identifying slow growth also captures this effect, because slow growth is a surrogate measure for low serum IGF-1. We hypothesize that a similar phenomenon will occur with the development of a new model, and consideration of other predictors will not be necessary.

The predicted outcome cases for the models are infants who developed ETROP type 1 or 2 ROP or are treated; the controls for the models are all remaining infants (infants who developed no ROP or ROP less severe than ETROP type 1 or 2 ROP).

Multiple ways of representing weight gain as a predictor will be considered, such as absolute and percentage changes from birth or previous week (weight gain rate), accumulated departures from "normal" weight gain, and standardized (Zscore) weights. Since numerous

weights will be measured for each infant, repeated measure logistic regression will be used to model the association of weight gain with severe ROP, PMA when postnatal weight was measured will also be included in the prediction model, and the correlation from repeated measures of weight gain will be accounted for by using the robust sandwich estimate.

Model performance will be assessed by calculating sensitivities and specificities for predicting two outcome measures, ETROP type 1 ROP and ETROP type 1 or 2 ROP, and calculating the percentage reduction in infants requiring examinations, which is a more clinically intuitive and relevant representation of specificity. An alarm cut point value of predicted probability will be set to maximize sensitivity at the cost of lower specificity, in an effort to minimize missed cases of severe ROP. However, multiple cut points will be assessed. Using the model, a probability of severe ROP will be calculated for each weekly postnatal weight gain rate, resulting in multiple predicted probabilities per infant. If a predicted probability is equal to or greater than the cut point, an alarm indicating a need for clinical exams is sounded.

Sensitivity will be calculated as the proportion of infants with alarms among infants with severe ROP. The 95% CI for sensitivity will be calculated with traditional normal approximation methods or the Clopper-Pearson exact method if the value is close to 100%.[32] The percentage reduction in the number of infants requiring eye examinations for varying alarm levels will be calculated as the proportion of infants not having alarms. Performance will be assessed secondarily using the time interval (in days) between first model alarm and severe ROP diagnosis, and multiple positive and negative predictive values will be calculated based on the range of severe ROP prevalence rates observed at the clinical centers.

Sample size—Sample size was driven by the precision of the point estimate of sensitivity for predicting severe ROP, as represented by the half-width of the 95% CI around that point estimate. This half-width CI, which determines the lower boundary of the CI, must necessarily be very small, ie, <1%, as current screening guidelines will not be changed without assurance that the model is very likely to continue to identify infants accurately who may require treatment. The CI must remain very small across the range of sensitivities that might be observed in the study. The model alarm threshold can be set low enough to attain very high sensitivity for severe ROP, preferably 100%, but slightly lower discrimination (98% or 99%) must be allowed for when calculating sample size. Table 1 shows the a priori sample size calculation for the G-ROP Study. The width of the CI is determined by the number of cases of severe ROP and the sensitivity estimate. If the cohort contains 800 cases of ETROP type 1 or 2 ROP, the half-width of the CI will be <1% for point estimates of sensitivity as low as 98%. Based on prior studies, we anticipated the rate of severe ROP to be 9.5% and that 85.5% of subjects would have a known ROP outcome and sufficient growth and medical data. With these assumptions, the target enrollment for the study was 9,850 infants.

RESULTS

The study data abstractors screened 11,261 infants (Table 2). Of infants screened, 8,334 infants met inclusion criteria and were enrolled in the study, and 2,927 had insufficient data

due to transfer to a non-study hospital, early discharge home, or death. Of the infants enrolled, 7,483 (90%) had a known ROP outcome and were included in the study dataset (Table 3). The median BW of evaluable infants was 1,070g (range 310–3,000g), and the median GA at birth was 28 weeks (range 22–35 weeks). There were no statistically significant differences between the BW and GA of infants with and infants without a known ROP outcome.

ROP developed in 3,224 (43.1%) infants (Table 4). Severe ROP (ETROP Type 1 or 2) developed in 933 (12.5%) infants, and 514 (6.9%) infants were treated for ROP. The severe ROP rate (12.5%) was higher than anticipated (9.5%); therefore, study enrollment was ended early, because the number of cases of severe ROP determined the statistical power, not the number of infants enrolled.

DISCUSSION

The G-ROP Study examines a large, racially and geographically diverse cohort of infants undergoing ROP screening in the US and Canada. The study will facilitate the development and evaluation of growth-based predictive algorithms to improve the efficiency of ROP screening, as well as provide descriptive data relating to the incidence and time course of ROP, ROP treatment and post-treatment complication rates, growth trajectories in premature infants, and incidence of and risk factors for various comorbidities of prematurity.

Model development is currently underway. The primary approach to model development mirrors the approach used in the PINT ROP and CHOP ROP studies. However, the performance of the existing CHOP ROP model itself will be assessed directly using the dataset, and alternative models will be considered as well. These approaches may include the cumulative deviations used by WINROP, in which differences between observed weight gain and expected weight gain, as derived from infants who do not develop ROP, are summed over time, and the simpler approach of the CO-ROP model, in which BW, GA, and weight gain at 1 month are evaluated only once to determine risk.[15, 17, 24] Additional strategies include: Altering examination timing and frequency based on predicted risk; defining cut-off levels of BW or GA beneath which all infants receive exams, and limiting risk assessment to larger, lower-risk infants; combining study data with costs data to determine the relative cost-effectiveness of varying approaches; and developing a multi-tiered ROP screening approach using additional modalities, such as fundus imaging, where the risk model determines a need for imaging, and trained-reader grading of images determines a need for examination by an ophthalmologist. As various algorithms are evaluated and a final G-ROP model developed, the parsimonious and simpler model will be preferred, in order to maximize the likelihood of physician acceptance and successful application to clinical practice. Finally, there may be outlier infants with severe ROP who can not be predicted by a weight-gain model; therefore, the analysis will include identification of confounding medical factors, such as sources of non-physiologic weight gain or high oxygen supplementation, the presence of which would exclude application of a growth-based predictive model and default an infant to receive eye examinations.

A critical feature of the G-ROP Study is the large sample size. The large number of cases of severe ROP provides statistical power to obtain highly precise estimates of sensitivity of the models being tested. Even with a risk "alarm level" set low enough to obtain 100% or near 100% sensitivity, the lower boundary of the CI around this point estimate of sensitivity arguably should be very high, greater than 99%, for physicians to have confidence that infants with severe ROP are unlikely to go undiagnosed. The G-ROP Study meets this goal; it affords a level of precision not provided by prior growth and ROP modeling studies. In addition, a large study cohort minimizes the chances of over fitting a prediction model during its development.[25, 33] Over fitting occurs when the complexity of the model is high relative to the number of outcome events in the study, so the model describes random error rather than a true association. Such a model will not perform well in new cohorts, so maximizing the size of the development cohort is essential.

Study data must be of high quality to be used as the basis for future high-stakes clinical decision-making. Therefore, numerous measures were taken to ensure the validity of the G-ROP Study data. Data collectors were subjected to a rigorous certification process. A feasibility study was completed to identify data consistently documented in the medical record and feasible to collect retrospectively without inference. In addition, extensive steps were taken to catch and correct data collection errors.

A limitation of the study is that ROP examinations were not performed in an a priori standardized fashion. However, the examinations reflect the reality and variety of clinical practice, and they were completed by ophthalmologists with expertise in ROP using standardized ICROP terms. Similarly, some data relevant to ROP and growth were not feasible to collect in great detail retrospectively, such as complex respiratory or nutritional measures. However, the primary study goal was to develop a predictive model that is implementable, and simplicity is important for successful widespread adoption. The simpler oxygen and nutritional data collected are a practical compromise, as more complicated measures are unlikely to be used clinically for ROP screening criteria.

Improved efficiency of ROP screening has numerous potential benefits. Revised screening guidelines and examination schedules could reduce the number of children requiring stressful eye examinations and the frequency of exams for at-risk infants. Professional and organizational resources then can be better allocated to high-risk infants, particularly in resource-limited areas. The cost effectiveness of ROP screening would also be increased. The G-ROP Study Group provides the largest currently available dataset with which to identify the most robust yet practical ROP risk algorithm, which eventually may be proposed as a replacement for current ROP screening guidelines.

Acknowledgments

Supported by National Institutes of Health grant 1R01EY021137–01A1. The sponsor or funding organization had no role in the design or conduct of this research.

Appendix A.: The Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study Administration and Clinical Centers. PI, principal investigator; Co-I, co-investigator.

Office of Study Chair - The Children's Hospital of Philadelphia

Chair: Gil Binenbaum, MD, MSCE

Project Manager: Lauren A. Tomlinson

Research Business Manager: Trang B. Duros

Data Coordinating Center - University of Pennsylvania School of Medicine

PI, Director: Gui-shuang Ying, Ph.D

Co-I: Maureen G. Maguire, Ph.D

Systems Analyst: Mary Brightwell-Arnold, BA, SCP

Biostatistician: James Shaffer, MS

Data Managers: Maria Blanco; Trina Brown

Clinical Data Management Director: Christopher P. Helker, MSPH

G-ROP Clinical Centers

Albany, NY - Albany Medical College

PI: Gerard P. Barry, MD

Co-I: Marilyn Fisher, MD, MS

Certified Data Collectors: Maria V. Battaglia; Alex M. Drach; Marilyn Fisher, MD, MS

Participating Hospitals: Albany Medical Center Hospital

Baltimore, MD - Johns Hopkins University

PI: Pamela Donohue, ScD

Co-I: Michael X. Repka, MD

Certified Data Collectors: Megan Doherty; Dorothy Dow; Jennifer A. Shepard, CRNP

Participating Hospitals: Johns Hopkins Hospital

Buffalo, NY - University at Buffalo

PI: James D. Reynolds, MD

Certified Data Collectors: Erin Connelly

Participating Hospitals: Women and Children's Hospital of Buffalo

Charleston, SC - Medical University of South Carolina

PI: Edward Cheeseman, MD MBA

Certified Data Collectors: Carol Bradham, COA, CCRC; Allison McAlpine; Sudeep Sunthankar; Kinsey Shirer, RN

Participating Hospitals: Medical University of South Carolina

Chicago, IL - University of Illinois at Chicago

PI: Javaneh Abbasian, MD

Certified Data Collectors: Janet Lim, MD

Participating Hospitals: University of Illinois at Chicago

Cincinnati, OH - Cincinnati Children's Hospital Medical Center

PI: Michael Yang, MD

Certified Data Collectors: Elizabeth L. Alfano; Patricia Cobb

Participating Hospitals: Cincinnati Children's Hospital Medical Center; Good Samaritan Hospital; University of Cincinnati Medical Center

Columbus, OH - Nationwide Children's Hospital

PI: David Rogers, MD

Certified Data Collectors: Rae R. Fellows, M.Ed., CCRC; Kaitlyn Loh; Madeline A. McGregor; Thabit Mustafa; Rachel E. Reem, MD; Tess Russell; Rebecca Stattler

Regulatory Coordinator: Sara Oravec

Participating Hospitals: Nationwide Children's Hospital

Honolulu, HI - Kapi'olani Medical Center for Women and Children

PI: David Young, MD Regulatory Coordinator: Andrea Siu, MPH, RAC

Certified Data Collectors: Michele Kanemori

Participating Hospitals: Kapi'olani Medical Center for Women and Children

Indianapolis, IN - Indiana University

PI: Jingyun Wang, PhD; Kathryn Haider, MD

Certified Data Collectors: Elizabeth Hynes, RNC-NIC

Participating Hospitals: Riley Hospital for Children at Indiana University Health

Iowa City, IA - University of Iowa

PI: Edward F. Bell, MD

Co-I: Alina V. Dumitrescu, MD and Jonathan M. Klein, MD

Certified Data Collectors: Avanthi S. Ajjarapu; Gretchen A. Cress, RN, MPH; Bethany M. Funk; Claire L. Johnson; Angela C. Platt

Participating Hospitals: University of Iowa Children's Hospital

Loma Linda, CA - Loma Linda University

PI: Leila Khazaeni, MD

Co-I: Jennifer Dunbar, MD

Certified Data Collectors: Kelley Hawkins; Sharon Lee, RN; Lily Sung

Participating Hospitals: Loma Linda University Children's Hospital

Louisville, KY - University of Louisville

PI: Rahul Bhola, MD

Certified Data Collectors: Michelle Bottorff, COA; Neviana Dimova, MD, MS; Rachel Keith, PhD, MSN, NP-C; Laura Thomas RN, BSN, CCRN

Participating Hospitals: Norton Kosair Children's Hospital

Minneapolis, MN - University of Minnesota

PI: Jill Anderson, MD

Certified Data Collectors: Jordan Gross; Ann Marie Holleschau, CCRP; Andrea Kramer

Participating Hospitals: Masonic Children's Hospital (formerly University of Minnesota - Amplatz Children's Hospital)

Nashville, TN - Vanderbilt Eye Institute and Vanderbilt University Medical Center

PI: David Morrison, MD

Co-I: Sean Donahue, MD, PhD

Certified Data Collectors: Neva Fukuda, CO; Sandy Owings, COA, CCRP; Scott Ruark

Participating Hospitals: Monroe Carell Jr. Children's Hospital at Vanderbilt

Oklahoma City, OK - University of Oklahoma

PI: R. Michael Siatkowski, MD

Co-I: Faizah Bhatti, MD

Regulatory Coordinators: Vanessa Bergman, COT, CCRC; Karen Corff, APRN, NNP

Certified Data Collectors: Kari Harkey, RNC-NIC; Amy Manfredo, APRN-CNP; Shrenik Talsania, MBBS, MPH, CPH; Terri Whisenhunt, MS, RN

Participating Hospitals: Children's Hospital at Oklahoma University Medical Center

Philadelphia, PA - The Children's Hospital of Philadelphia

PI: Gil Binenbaum, MD, MSCE

Co-I: Haresh Kirpalani, MD, MSc; Graham E. Quinn MD, MSCE

Certified Data Collectors: Lindsay Dawson, MD; Lauren A. Tomlinson

Participating Hospitals: The Children's Hospital of Philadelphia; Hospital of the University of Pennsylvania

Providence, RI - Rhode Island Hospital

PI: Wendy S. Chen, MD, PhD

Certified Data Collectors: Deidrya Jackson

Participating Hospitals: Women and Infants Hospital of Rhode Island

Saint Louis, MO - Saint Louis University

PI: Bradley Davitt, MD

Regulatory Coordinator: Dawn Govreau, COT

Certified Data Collectors: Linda Breuer, LPN; September Noonan, RN

Participating Hospitals: Cardinal Glennon Children's Hospital

Salt Lake City, UT - University of Utah

PI: Robert Hoffman, MD

Co-I: Joanna Beachy, MD, PhD

Regulator Coordinator: Deborah Harrison, MS

Certified Data Collectors: Ashlie Bernhisel; Bonnie Carlstrom; Katie Jo Farnsworth, CRC

Participating Hospitals: Primary Children's Hospital; University of Utah Hospital

San Francisco, CA - University of California, San Francisco

PI: Alejandra G. de Alba Campomanes, MD, MPH

Regulatory Coordinator: Jacquelyn Kemmer

Certified Data Collectors: Alexandra Neiman; Sarah Sitati-Ng'Anda MD

Participating Hospitals: Zuckerberg San Francisco General Hospital (formerly San Francisco General Hospital); UCSF Benioff Children's Hospital

Seattle, WA - Seattle Children's Hospital

PI: Francine Baran, MD; Kristina Tarczy-Hornoch, MD, D.Phil

Certified Data Collectors: Lauren Eaton

Participating Hospitals: University of Washington Medical Center

Toronto, Ontario, Canada - The Hospital for Sick Children (Sick Kids)

PI: Nasrin Najm-Tehrani, MD, MSc

Certified Data Collectors: Maram Isaac; Robin Knighton

Participating Hospitals: The Hospital for Sick Children (Sick Kids)

Torrance, CA - Los Angeles Biomedical Research Institute

PI: Monica Ralli Khitri, MD

Certified Data Collectors: Madeline Del Signore, RN

Participating Hospitals: Harbor-UCLA Medical Center

Upland, PA - Crozer-Chester Medical Center

PI: Cynthia Dembofsky, MD; Andrew Meyer, MD

Certified Data Collectors: Cynthia Dembofsky, MD; Karen Flaherty; Tracey Harris; Jamie Heeneke

Participating Hospitals: Crozer-Chester Medical Center

Wilmington, DE - Nemours/Alfred I. duPont Hospital for Children

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Appendix B.: Search terms to identify retinopathy of prematurity (ROP) data collection or entry errors. All examinations flagged with one or more search terms were rechecked with the primary source data for potential data collection error. PMA, postmenstrual age. APROP, aggressive posterior ROP.

1. Timing of ROP
    a. An eye with first occurrence of
        i. Stage 1 prior to PMA 30
        ii. Stage 2 prior to PMA 31
        iii. Stage 3 prior to PMA 32
        iv. Stage 4A prior to PMA 37
        v. Stage 4B prior to PMA 37
        vi. Stage 5 prior to PMA 37
        vii. Type 1 ROP prior to PMA 32 weeks
        viii. Type 2 ROP prior to PMA 31 weeks
        ix. Plus disease prior to PMA 32 weeks
        x. Plus disease after PMA 43 weeks
        xi. Treatment before PMA 32 weeks
        xii. Treatment after PMA 46 weeks
        xiii. APROP after PMA 36 weeks
        xiv. Regressing prior to PMA 33 weeks
        xv. Regressing after PMA 50 weeks
        xvi. Regressed prior to PMA 35 weeks
        xvii. Mature prior to PMA 33 weeks
        xviii. Zone 2 prior to PMA 30 weeks
        xix. Zone 3 prior to PMA 33 weeks

b. An eye with any occurrence of

i. Stage 0 after PMA 53 weeks

ii. Stage 1 after PMA 53 weeks

iii. Stage 2 after PMA 53 weeks

iv. Stage 3 after PMA 50 weeks

v. Regressing (Stage 6) after PMA 53 weeks

vi. Zone 2 after PMA 59 weeks

vii. Plus prior to PMA 31 weeks

viii. Plus after PMA 55 weeks

ix. Pre-plus after PMA 55 weeks

2. Disease course of ROP

a. First occurrence of "Mature" for a single eye is followed by another eye exam for that eye

b. Any eye that has a diagnosis of "regressed" has not be preceded with examination demonstrating stage 1, 2, or 3

3. Laterality of ROP

a. One eye has stage 0 and the other eye has stage 2 or 3

b. One eye has stage 1 and the other eye has stage 3

4. Treatment and severe ROP

a. Type 1 ROP without treatment

b. ROP treatment with no ROP or less severe ROP than type 1 ROP

c. ROP treatment without stage, zone, or plus diagnosis

d. All stage 4 or 5 ROP diagnoses

e. AP-ROP or plus disease diagnosis without stage or zone specified

f. Plus disease diagnosis with "regressing" ROP or without a stage and zone

g. Plus disease diagnosis without other criteria for type 1 ROP

h. Plus disease or stage 3 ROP in zone III

i. Type 1 or 2 ROP diagnosed in infant 28 or greater weeks GA or BW 1000 g or more

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Table 1.

Precision of sensitivity for predicting severe retinopathy of prematurity (ROP) for the proposed sample size of the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study

Sensitivity of model	Sample size, n		Cases severe ROP	Sensitivity 95% CI		Half width of 95% CI
	Enrolled	Evaluable		Lower bound	Upper bound	
100%	9.850	8,422	800	99.5%	100%	**0.24%**
99%	9.850	8,422	800	98.0%	99.5%	**0.73%**
98%	9,850	8,422	800	96.8%	98.8%	**0.99%**

CI, confidence interval.

Table 2.

Characteristics of screened, enrolled, and non-enrolled infants in the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study.

Characteristic	Total screened (n=11,261)	Enrolled (n=8,334)	Non-enrolled (n=2,927)	P-value
Birth weight, g				
Mean (SD)	1,122 (399)	1,193 (493)	1,099 (359)	<0.001
Median (Q1,Q3)	1,085 (803,1,400)	1,170 (770,1,570)	1,070 (815,1,350)	
Gestational age, weeks				
Mean (SD)	28.1 (2.8)	28.3 (3.2)	28.0 (2.6)	<0.001
Median (Q1,Q3)	28 (26,30)	29 (26,31)	28 (26,30)	
Sex, n (%)				
Female	5,307 (47.1)	1,327 (45.4)	3,980 (47.8)	0.03
Male	5,952 (52.9)	1,598 (54.6)	4,354 (52.2)	
Maternal ethnicity, n (%)				
Hispanic or Latino	834 (7.4)	195 (6.7)	639 (7.7)	<0.001
Not Hispanic or Latino	6,822 (60.6)	1,111 (38.0)	5,711 (68.5)	
Unknown	3,605 (32.0)	1,621 (55.4)	1,984 (23.8)	
Maternal race, n (%)				
White/Caucasian	5,129 (45.6)	1,150 (39.3)	3,979 (47.8)	<0.001
Asian/Asian American	343 (3.1)	79 (2.7)	264 (3.2)	
Black/African American	3,161 (28.1)	662 (22.6)	2,499 (30.0)	
American Indian/Alaskan Native	56 (0.5)	14 (0.5)	42 (0.5)	
Native Hawaiian/other Pacific Islander	122 (1.1)	20 (0.7)	102 (1.2)	
Other	771 (6.9)	246 (8.4)	525 (6.3)	
Unknown	1,571 (14.0)	739 (25.3)	832 (10.0)	
Birth location, n (%				
Inborn	7,490 (66.5)	1,394 (47.6)	6,096 (73.1)	<0.001
Outborn	3,771 (33.5)	1,533 (52.4)	2,238 (26.9)	

SD, standard deviation; Q1, first quartile; Q3, third quartile.

Table 3.

Characteristics of evaluable, and non-evaluable infants in the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study.

Characteristic	All enrolled (n=8,334)	Evaluable (n=7,483)	Non-evaluable (n=851)	P-value
Birth weight, g				
≤500, n (%)	121 (1.5)	112 (1.5)	9 (1.1)	
500–750, n (%)	1,463 (17.6)	1,341 (17.9)	122 (14.3)	
751–900, n (%)	1,235 (14.8)	1,098 (14.7)	137 (16.1)	
901 1,000, n (%)	804 (9.6)	707 (9.4)	97 (11.4)	
1,001 1,100, n (%)	815 (9.8)	725 (9.7)	90 (10.6)	
1,101 1,200, n (%)	1,156 (13.9)	1,011 (13.5)	145 (17.0)	
≥1,251, n (%)	2,740 (32.9)	2,489 (33.3)	251 (29.5)	
Mean (SD)	1,100 (363)	1,099 (359)	1,088 (321)	0.37
Median (Q1,Q3)	1,070 (810,1,358)	1,070 (815,1,350)	1,070 (840,1,300)	
Median (min, max)	1,070 (310,3,000)	1,070 (310,3,000)	1,070 (372,2,330)	
Gestational age, weeks				
22, n (%)	18 (0.2)	17 (0.2)	1 (0.1)	
23, n (%)	232 (2.8)	217 (2.9)	15 (1.8)	
24, n (%)	615 (7.4)	563 (7.5)	52 (6.1)	
25, n (%)	751 (9.0)	691 (9.2)	60 (7.1)	
26, n (%)	912 (10.9)	801 (10.7)	111 (13.0)	
27, n (%)	1,000 (12.0)	884 (11.8)	116 (13.6)	
28, n (%)	1,119 (13.4)	962 (12.9)	157 (18.4)	
29, n (%)	1,006 (12.1)	879 (11.7)	127 (14.9)	
30, n (%)	1,117 (13.4)	1,029 (13.8)	88 (10.3)	
31, n (%)	878 (10.5)	798 (10.7)	80 (9.4)	
≥32, n (%)	686 (8.2)	642 (8.6)	44 (5.2)	
Mean (SD)	28 (3)	28 (3)	28 (2)	0.20
Median (Q1,Q3)	28 (26,30)	28 (26,30)	28 (26,29)	
(min, max)	(22,35)	(22,35)	(22,34)	
Sex, n (%)				
Female	3,980 (47.8)	3,575 (47.8)	405 (47.6)	0.94
Male	4,354 (52.2)	3,908 (52.2)	446 (52.4)	
Maternal ethnicity, n (%)				
Hispanic or Latino	639 (7.7)	564 (7.5)	75 (8.8)	<0.001
Not Hispanic or Latino	5,711 (68.5)	5,251 (70.2)	460 (54.1)	
Unknown	1,984 (23.8)	1,668 (22.3)	316 (37.1)	
Maternal race, n (%)				
White/Caucasian	3,979 (47.8)	3,615 (48.4)	364 (42.8)	<0.001
Asian/Asian American	264 (3.2)	233 (3.1)	31 (3.6)	
Black/African American	2,499 (30.0)	2,310 (30.9)	189 (22.2)	
American Indian/Alaskan Native	42 (0.5)	40 (0.5)	2 (0.2)	

Characteristic	All enrolled (n=8,334)	Evaluable (n=7,483)	Non-evaluable (n=851)	P-value
Native Hawaiian/other Pacific Islander	102 (1.2)	93 (1.2)	9 (1.1)	
Other	525 (6.3)	442 (5.9)	83 (9.8)	
Unknown	832 (10.0)	666 (8.9)	166 (19.5)	
Birth location, n (%)				
Inborn	6,096 (73.1)	5,512 (73.7)	584 (68.6)	0.002
Outborn	2,238 (26.9)	1,971 (26.3)	267 (31.4)	

SD, standard deviation; Q1, first quartile; Q3, third quartile; min, minimum; max, maximum.

Table 4.

Retinopathy of prematurity (ROP) characteristics of evaluable babies in the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study

Characteristic	Category	Evaluable, n (%) (n=7,483)
Any stage ROP	Yes	3,224 (43.1)
	No	4,259 (56.9)
Type of ROP	Type 1 ROP	459 (6.1)
	Type 2 ROP	472 (6.3)
	ROP, not type 1, 2	2,293 (30.6)
	No ROP	4,259 (56.9)
ROP treatment	Yes	514 (6.9)
	No	6,969 (93.1)
Highest stage of ROP	No ROP	4,259 (56.9)
	1	1,398 (18.7)
	2	1,002 (13.4)
	3	821 (11.0)
	5	3 (0.04)
Lowest zone of ROP	I	147 (2.0)
	II	2,637 (35.2)
	III	433 (5.8)
	Not Specified	7 (0.1)
	No ROP	4,259 (56.9)
Plus disease	None	6,706 (89.6)
	Pre-Plus	337 (4.5)
	Plus	440 (5.9)