**Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)**
Part I

| Author, Year<br>UI# | Demographics | Inclusion Criteria | Exclusion Criteria | Disease/Condition<br>Type (N) | Study Design<br>(Duration) |
|---|---|---|---|---|---|
| Cryo-ROP,<br>1990, 1996, and 2001 (x3)<br>91024693,<br>96180078,<br>21375786,<br>21375787,<br>21375788<br><br>Repka<br>1998<br>98426775<br><br>***sample from the large population of 94304375 (CRYO-ROP)** | Location: US<br>Years of Birth: from 1/1986 to 11/1987<br>Mean GA (range), wk:<br>1 yr follow-up: 26.3±1.8<br>5.5 yr follow-up: 26.3±1.7 (bilateral threshold ROP; 26.3±1.8 (asymmetric threshold ROP)<br>10 yr follow-up: 26.3±1.8<br>Mean BW(range), g:<br>1 yr follow-up: 800±165<br>5 yr follow-up: 801±165 (bilateral threshold ROP; 800±165 (asymmetric threshold ROP)<br>10 yr follow-up: 800±165<br>Male: ND<br>Race: ND<br>Enrolled: 291<br>Evaluated: 246 (at 1-year exam), 234 (at 5.5-year exam), 247 (at 10-year exam)<br>Number of sites: 23 | BW < 1251 g<br>Survived at least 28 days<br>Diagnosis of threshold ROP | ND<br>{(At 1-year follow-up:<br>Died before the 1-year follow-up (36)<br>Unable to follow-up for the 1-year exam (14)<br>At 5.5-year & 10-year follow-up:<br>Died before the 5.5-year & 10-year exam (36)}<br>Lost to follow-up for the 10-year exam (8) | At 1-year exam: VLBW infants with ROP (241)<br>At 5.5-year exam: VLBW infants with ROP (234) – bilateral threshold ROP (191); asymmetric threshold ROP (43)<br>At 10-year exam: VLBW infants with ROP (234) | Randomized controlled trial<br>(1, 5.5, 10 years) |
| Cryotherapy for Retinopathy of Prematurity Group<br>1993<br>93191597 | Location: US<br>Years of Birth: 1986-1987<br>Mean GA (range), wk: 26.3±1.8<br>Mean BW (range), g: 800±165<br>Male: ND<br>Race: ND<br>Enrolled: 236<br>Evaluated: 236<br>Number of sites: 23 | All infants <1251g, who participated in CRYO-ROP Multicenter trial and had threshold (severe) ROP. | See original study | Infants with threshold ROP (236) | 3.5 years |

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Part I

| Author, Year<br>UI# | Demographics | Inclusion Criteria | Exclusion Criteria | Disease/Condition<br>Type (N) | Study Design<br>(Duration) |
|---|---|---|---|---|---|
| Algawi<br>1994<br>95001766 | Location: UK<br>Years of Birth:<br>Sample 1: 2/1992-11/1992<br>Sample 2: 1/1987-2/1992<br>Mean GA (range), wk:<br>Sample 1: 24-32<br>Sample 2: 25-30<br>Mean BW (range), g:<br>Sample 1:700-1200<br>Sample 2: 620-1500<br>Male: 53%<br>Race: ND<br>Enrolled: 32<br>Evaluated: 32<br>Number of sites: 1 | Premature infants with threshold ROP (stage 3+ disease of 5 or more contiguous clock hours [30° sector] or 8 cumulative clock hours) or more | ND | Sample 1: Laser Treatment (12)<br>Sample 2: Cryotherapy Treatment (20) | Prospective cohort |
| Ling<br>1995<br>95391616 | Location: UK<br>Years of Birth: 1992-1993<br>Median GA (range), wk: 25.5 (24-27)<br>Median BW (range), g: 725 (589-887)<br>Male: 38%<br>Race: White 100%<br>Enrolled: 13<br>Evaluated: 13<br>Number of sites: 1 | All premature infants in 1 unit who developed threshold ROP and treated with diode laser therapy | ND | Infants with ROP treated with Diode laser (13) | Before and after trial (6, 12, and 18 months) |

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| Author, Year<br>UI# | Demographics | Inclusion Criteria | Exclusion Criteria | Disease/Condition<br>Type (N) | Study Design<br>(Duration) |
|---|---|---|---|---|---|
| Connolly<br>1998<br>984267776 | Location: US<br>Years of Birth: 11/1989-5/1992<br>Mean GA (range), wk: 25.4 (23-32)<br>Mean BW (range), g: 731 (440-1318)<br>Male: 44%<br>Race: ND<br>Enrolled: 52<br>Evaluated: 25<br>Number of sites: 1 | Premature infants with symmetric threshold ROP underwent bilateral treatment | ND<br>(Stage 4 or 5 ROP in one or both eyes<br>Refused to cooperate with monocular occlusion during Snellen testing<br>Limited cognitive ability that precluded Snellen or illiterate e-chart acuity testing) | Sample 1: Laser Treatment (21 eyes)<br>Sample 2: Cryotherapy Treatment (21 eyes) | RCT and follow-up<br>(5.8 [4.3-7.6] years) |
| Shalev<br>2001<br>21331013 | Location: US<br>Years of Birth: 1991-1992<br>Mean GA (range), wk: 24.8 (23.4-27.0)<br>Mean BW (range), g: 631 (540-846)<br>Male: 60%<br>Race: 30%<br>Enrolled: 19<br>Evaluated: 10<br>Number of sites: 1 | Threshold ROP treated with laser or cryotherapy | ND<br><br>Lost to follow-up (2)<br>Died at 4 months of age (2)<br>Refusal (3) | Infants with threshold ROP (10) | RCT with prospective follow-up<br>(7 years and 6 months) |
| O'Connor<br>2002<br>21635822 | Location: UK<br>Years of birth: 1985-1987<br>Mean GA (range), wk: 31.06±3.09<br>Mean BW (range), g: 1400 (iqr 1150, 1562)<br>Male: ND<br>Race: ND<br>Enrolled: 505<br>Evaluated: 505<br>Number of sites: 5 | All infants <1701g, who survived 3 weeks. Born to mothers who were residents in the study areas, admitted to one of 5 NICUs. | ND | Premature infants (254)<br>Control (169) | 10-12 years |

**Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)**
Part II

| Author, Year | Predictors | Predictor Measures | Outcomes | Outcome Measures |
|---|---|---|---|---|
| Cryo-ROP, 1990, 1996, and 2001 (x3)<br>91024693, 96180078, 21375786, 21375787, 21375788<br><br>Repka 1998<br>98426775<br><br>***sample from the large population of 94304375 (CRYO-ROP)** | *Ophthalmology predictors:*<br>Threshold retinopathy of prematurity<br><br>At 5.5-year & 10-year follow-up:<br>Cryotherapy vs. No Cryotherapy | At least 5 contiguous clock hours or 8 cumulative clock hours of stage 3 ROP in zone 1 or 2 in the presence of "plus disease" (dilation and tortuosity of the posterior retinal vessels)<br>Monocular visual acuity (using log of minimal angle of resolution visual acuity chart) | **Ophthalmology:**<br>Visual impairment (visual acuity)<br>Structural outcome<br>Blindness<br>Distance snellen acuity<br>Near snellen acuity<br>Visual field<br>Medical and surgical ophthalmologic interventions<br>Cerebrospinal fluid shunting surgery | Visual acuity -<br>• "normal": ?1.6 cycles per degree<br>• "below normal": 8.0 to <1.6 cycles per degree<br>• "poor": <0.8 cycles per degree<br>• "blind": eyes judged to have no light perception, eyes for which the tester was unable to estimate acuity, which were judged by a physician to have total retinal detachment<br>Structural outcome -<br>• Posterior retinal fold<br>• Retinal detachment involving zone 1 of the posterior pole<br>• Retrolental tissue or "mass" obscuring the view of the posterior pole<br>Favorable Functional outcome:<br>Favorable visual acuity: better than 20/200<br>Unfavorable visual acuity: worse than 20/200 or blind<br>Goldmann perinmetry to measure visual field extent along 8 meridian using V4e and III 4 e stimuli |
| Cryotherapy for Retinopathy of Prematurity Group 1993<br>93191597 | Retinopathy of Prematurity (ROP) (Specifically threshold ROP treated with cryotherapy or no cryotherapy) | Threshold ROP as per CRYO-ROP definition. | **Visual impairment**<br>Blindness | Visual acuity (HOTV, Grating)<br>Unfavorable outcome (HOTV 20/200 or worse, Grating <6.4 cycles per degree; blind): this outcome is combination of poor + blind<br>Myopia:≥2 <6 diopters; ≥6 diopters |

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Part II

| Author, Year | Predictors | Predictor Measures | Outcomes | Outcome Measures |
|---|---|---|---|---|
| Algawi<br>1994<br>95001766 | Ophthalmology<br>Retinopathy | ND | **Ophthalmology:**<br>Visual impairment:<br>Refractive error<br>Visual fixation<br>Preferential looking | Visual functions were assessed by either fixation pattern or preferential looking technique |
| Ling<br>1995<br>95391616 | ROP | Threshold as for Cryo-ROP trial | **Ophthalmology**<br>Visual function | Favorable outcome (anatomical) defined as a normal posterior funus on BIO exam performed by observer who had not done Rx. Functional outcomes assessed using Keeler preferential looking cords acuity greater or equal to 0.8 cycles per degger defined 1 yr. Age<br>. |
| Connolly<br>1998<br>984267776 | ROP | Threshold as for Cryorop trial - 5 or more contiguous or 8 cumulative clock-hours of stage 3 ROP in zone I or II in the presence of “plus” disease | **Ophthalmology Outcomes:**<br>Visual impairment<br>Refractive error<br>Visual acuity | Visual acuity 20/50 or better =good<br>Visual acuity 20/60 or worse = poor |
| Shalev<br>2001<br>21331013 | ROP | Threshold as for Cryorop trial | **Ophthalmology**<br>Visual function outcome<br>Structural outcome | Favorable outcome = normal posterior fundus.<br>Refraction by retinoscopy<br>Functional outcomes: Keeper preferential looking cards . Favorable function was grating acuity greater than or equal to 0.8 cycles/degree (as per CRYO ROP study at 1 year) |

**Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)**
Part II

| Author, Year | Predictors | Predictor Measures | Outcomes | Outcome Measures |
|---|---|---|---|---|
| O'Connor 2002 21635822 | Birth weight<br>ROP | BW self-explanatory (grams)<br>ROP not stated, but c/w ICROP | **Visual impairment**<br>Blindness | Visual acuity: Normal (20/20); ≥Moderately reduced = worse than 20/40.<br>Contrast sensitivity (Pelli Robson chart)<br>Steroacuity (TNO plates)<br>Perimetry (visual fields) (Damato campimeter)<br>Color vision (desaturated D15 test)<br>Strabismus (cover test and prism test)<br>Refractive error (cycloplegic refraction)<br>Eye size and dimensions of its components (N.D.) |

**Evidence Table 8. Studies of Treatment Effects for LBW Infants with Retinopathy of Prematurity (ROP)**
Part III

| Author, Year | Associations found | Potential Biases | Comments |
|---|---|---|---|
| Cryo-ROP, 1990, 1996, and 2001 (x3)<br>91024693, 96180078, 21375786, 21375787, 21375788<br><br>Repka 1998<br>98426775<br><br>***sample from the large population of 94304375 (CRYO-ROP)** | **At 1-year follow-up:**<br>Fundus photography: Unfavorable posterior pole outcome at 1 yr<br>Cryotherapy Rx 191 eyes 25.7%<br>Control 194 eyes 47.4% P<0.001<br>Unfavorable structural outcome (retinal detachment, macular fold, etc) at 1 yr<br>Cryotherapy Rx 208 eyes 49%<br>Control 203 eyes 66%<br>Unfavorable functional (Teller Visual Acuity) outcome at 1 yr<br>Cryotherapy Rx 160 35%<br>Control 158 56.3%<br>**At 5.5-year follow-up:**<br>Visual acuity Unfavorable outcome:<br>Threshold ROP (control: no cryotherapy) 62%<br>Threshold ROP CRYOtherapy 47%<br>Greater reduction in unfavorable visual acuity outcome in cryo group (P<0.005)<br>**Unfavorable structural outcome**<br>Threshold ROP (control: no cryotherapy) 45%<br>Threshold ROP CRYOtherapy 27%<br>Greater reduction in unfavorable structural outcome in cryotherapy group (P<0.001)<br>**Blindness**<br>Threshold ROP (control: no cryotherapy) 48%<br>Threshold ROP CRYOtherapy 32%<br>Greater reduction in blindness in cryotherapy group (P<0.001)<br>**Visual acuity 20/40 or better**<br>Threshold ROP (control: no cryotherapy) 17%<br>Thresdhold ROP CRYOtherapy 13%<br>No significant difference between groups with respect to proporation of infants with visual acuity 20/40 or better (P=0.19).<br>Among children who had Threshold ROP treated with cryotherapy: 226 / 257 had ocular intervention in addition to cryotherapy (0.9% interventions per child) Vitrectomy 26% (66/257); Scleral buckling 3% (8/257); Lensectomy 18%; Glaucoma medical treatment 4%; Glucoma surgery 2%; amblopia treatment 20%; Strabismus surgery 10%; Cataract surgery 2%; Enucleation 2%; Ventriculoperitoneal shunt (VPS) 11% Among children in the Natural History Cohort with variable ROP: 239 ocular interventions (0.4% interventions per child) Strabismus 6%; Amblyopia Rx 7% (3% if no ROP); VPS 3% | (None) | Study was government and private funded 5 ½ year follow-up of preterm infants with BW <1251 g with Threshold ROP randomized to cryotherapy vs. no cryotherapy groups. Both had high incidence of blindness, impaired visual acuity, and unfavorable outcome. Unfavorable outcomes were significantly less in cryotherapy group vs. control group. Excellent long-term (10 yr) ophthalmic follow-up of PT infants with severe ROP. Cryotherapy assoc with significantly less unfavorable visual function outcome and less unfavorable structural outcome. >44% of cryo Rx eyes have unfavorable visual outcome and 62% have unfavorable structural outcome. Threshold ROP with or without Rx is high for adverse long-term outcome. Infants with BW<1251 g with ROP underwent a large number of ophthalmic interventions through the first 5.5 years of life. Long-term costs of extreme prematurity and ROP include initial ablative therapy for ROP and societal loss due to visual impairment or blindness and ongoing costs for caring for eye problems. |

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Part III

| Author, Year | Associations found | Potential Biases | Comments |
|---|---|---|---|
| Cryo-ROP, 1990, 1996, and 2001 (x3) 91024693, 96180078, 21375786, 21375787, 21375788 | **At 10-year follow-up:**<br>**Unfavorable** Visual outcomes (functional) in Threshold ROP. Comparison of Threshold ROP eyes treated with CRYO vs. Control.<br>Distance Snellen Acuity (≥20/200)<br>CRYO Rx 44%<br>Control 62%<br>Near Snellen Acuity<br>CRYO Rx 43%<br>Control 62% | | |
| Repka 1998 98426775 | Blindness<br>CRYO Rx 33%<br>Control 50%<br>Unfavorable Visual Acuity<br>Zone I/Threshold ROP/ CRYO Rx 94%<br>Zone I/Threshold ROP/Control 94%<br>Unfavorable structural outcome<br>Zone I/Threshold ROP/ CRYO Rx 88%<br>Zone I/Threshold ROP/Control 94%<br>Although cryotherapy was beneficial in reducing unfavorable structural and functional outcome vs. no treatment in Threshold ROP eyes, infants with threshold ROP still were at high risk for unfavorable outcome even with cryotherapy, especially infants with Threshold Zone 1 ROP.Vii<br>Visual fields at 10 years age in children enrolled in the CRYO ROP trial who had history of Threshold ROP (cryotherapy vs. control). Visual fields (with or without cryotherapy) were significantly smaller with severe ROP Visual fields in treated eyes were reduced by 30-37% vs. no ROP. Visual fields in control eyes were reduced by 27-33% compared to no ROP. Cryotherapy vs. control preserved sight and visual field in infants with severe ROP. Visual field area was 24 to 26% larger in CRYO Rx eyes vs. Control. Comparison of sighted treated eyes vs. sighted control eyes revealed that cryotherapy reduced visual field by small amount (5%). | | |
| **Continued** | | | |

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Part III

| Author, Year | Associations found | | | | | | Potential Biases | Comments |
|---|---|---|---|---|---|---|---|---|
| | **Predictors/ Conditions** | **N** | **Outcome Category** | **Outcome of Interest/ Instruments used** | **% with Outcome** | **Methods of Correlation** | | |
| Cryotherapy for Retinopathy of Prematurity Group 1993 93191597 | Cryotherapy | 203 | vision | Unfavorable outcome HOTV acuity | 47% | Cryo group had 19% reduction in unfavorable outcome for HOTV (p<0.01) | | |
| | No Cryotherapy | 203 | vision | Unfavorable outcome HOTV acuity | 58% unfavor-able outcome | | | |
| | Cryotherapy | 193 | vision | Unfavorable outcome Grating acuity | 52% | Cryo group had 20% reduction in unfavorable outcome for grating (p<0.01) | | |
| | No Cryotherapy | 193 | vision | Unfavorable outcome Grating acuity | 66% | | | |
| | Cryotherapy | | vision | Myopia **: ³ 2 <6 diopters** | 20% | More treated eyes had myopia than control eyes. Data not shown is that more control eyes could not be refracted. | | |
| | No Cryotherapy | | vision | Myopia **: ³ 2 <6 diopters** | 15.5% | | | |
| | Cryotherapy | | vision | **Myopia ³ 6 diopters** | 37.7% | | | |
| | No Cryotherapy | | vision | Myopia **: ³ 6 diopters** | 27.2% | | | |

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| Algawi<br>1994<br>95001766 | Myopia<br>Treat with Laser 6/15 (40%) (Spher Equiv –1.5 to –3.5 D)<br>Treat with Cryotherapy 23/25 (92%) (Spher Equiv –0.5 to –8.0 D)<br>Significantly more myopia in cryotherapy vs. laser group (P=0.0006)<br>Hypermetropia <+3.0 Diopters<br>Treat with Laser 9/15 (60%)<br>Treat with Cryotherapy 2/25 (8%)<br>Clinical significant astigmatism (no significant difference between groups (P=0.4).<br>Treat with Laser 5/15<br>Treat with Cryotherapy 5/25 | Small sample size<br>Cohorts treated at different time, not concurrent and not randomized | No data on funding source<br>There is a high incidence of myopia following treatment for threshold ROP. Myopia occurred less often in the laser treated group vs. cryotherapy treated group. |
| Ling<br>1995<br>95391616 | Visual outcome of Threshold ROP treated with diode laser: Structural Outcome (as defined by Cryotherapy Multicenter Trial) at 19.5 months age (range 9.7-25.5. mo) was favorable in all 13 patients (25 eyes). Functional outcome at the same follow-up (n=13): 3 with strabismus; 1 myopic; grating visual acuity (Keeler preferential looking cards) ranged 2.9-14.5 cycles per degree. 7 uniocular and 6 binocular acuity assessments fell within the CRYO-ROP definition of favorable acuity at 1 year of age (≥0.8 cycles per degree uniocular) | (None) | No data on funding source |

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| Connolly 1998 984267776 | Laser Treated Threshold ROP / Cryotherapy Treated Threshold ROP / Total<br>Visual Acuity 20/50 or better: 17 / 8 / 25<br>Visual Acuity 20/60 or worse: 4 / 13 / 17<br>Total: 21 / 21 / 42<br><br>81% of laser-treated vs. 38 % of cryotherapy treated Threshold ROP had good visual acuity outcome (VA 20/50 or better). The odds that a laser treated eye had a good visual outcome were 6.91 greater than threshold ROP eyes treated with cyrotherapy (95% CI 1.7- 28).<br>Refractive Error: On average, 23 cryotherapy eyes had a mean spherical equivalent of – –5.08 Diopters vs. –3.05 Diopters for 23 laser treated eyes P=0.0072). Thus, cryotherapy eyes had greater amount of myopia than laser treated eyes.<br><br>Summary: The odds that eyes treated with laser therapy would have best-corrected visual acuity of 20/50 or better was almost 7 times greater than cryotherapy treated eyes. Also, laser treated eyes had less myopia than cryotherapy treated eyes. Thus, the results suggest that laser photocoagulation for threshold ROP was more likely to result in good visual outcome with less myopia compared to cryotherapy treatment. | Excluded large numbers of subjects | No data on funding source |
| Shalev 2001 21331013 | **Associations:**<br>All 10 Laser treated eyes had favorable structural outcome; 2 of 8 cryotherapy eyes had unfavorable structural outcome.<br><br>Laser-treated vs. cryotherapy treated threshold eyes had more favorable outcome.<br>Laser / Cryotherapy / P<br>Geometric visual acuity: 20/33 / 20/133 / 0.03<br>Range: (20/20-20/70) / (20/25 to phthisis)<br>Mean refractive error(D): -6.5 / -8.25 / 0.27<br><br>Conclude: Laser therapy for threshold ROP may have long-term visual function advantages over cryotherapy. | Small numbers for randomized comparison.<br>It is not clear how similar were the groups in terms of original threshold ROP (zone I vs. II) | No data on funding source |

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Part III

| Author, Year | | Associations found | | | | | | Potential Biases | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | **Predictors/Conditions** | **N** | **Outcome Category** | **Outcome of Interest/ Instruments used** | **% with Outcome** | **Methods of Correlation** | | |
| O'Connor 2002 21635822 | **Full term** | Control | 169 | Visual function | Distance Acuity (Left eye) | -0.08 (-0.1,0.01) | | | |
| | **BW <1701 all** | Premature cohort | 254 | Visual function | Distance Acuity (Left eye) | 0.0 (-0.08,0.1) | | | |
| | No ROP | Premature cohort | 126 | Visual function | Distance Acuity (Left eye) | 0.0(-0.08,0.04) | | | |
| | Stage 3 or 4 ROP | Premature cohort | 7 | Visual function | Distance Acuity (Left eye) | 0.34(0.21,0.605) | | | |
| | **Full term** | Control | 169 | Visual function | Binocular Distance Acuity | Normal 93% ≥Moderately reduced 0% | P<0.001 between control vs. premature cohort | | |
| | **BW <1701 all** | Premature cohort | 254 | Visual function | Binocular Distance Acuity | Normal 76% ≥Moderately Reduced 3.5% | | | |