

**Cycled Phototherapy: A Safer Effective Method to Control
the Serum Bilirubin of Extremely Premature Infants?**

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Note: Study Forms will be included in conjunction with the Manual of Operations

Section 1. Synopsis

Rationale. Were they not delivered early, extremely premature infants would normally develop in darkness within the uterus for 3-4 more months longer before birth. Yet, the routine care of these infants has involved the use of uninterrupted (continuous) exposure to bright light during phototherapy (**PT**), a treatment method that neonatologists have assumed has no serious adverse effects on even the most immature of newborns. As indicated below, this assumption is neither evidence-based nor biologically plausible.

Evidence from randomized trials that continuous PT increases the mortality of small premature babies. There is only one large randomized trial comparing PT to no PT: the NICHD Collaborative PT Trial which assessed continuous PT in treating infants enrolled during the 1970s. Contrary to the primary hypothesis, no neurodevelopmental benefits of PT were identified. Moreover, the findings were compatible with a 32% increase in mortality among all LBW infants (relative risk [**RR**] for death with PT = 1.32; 95% confidence interval = 0.96-1.82) and a 49% increase among infants ≤ 1000 g BW (RR = 1.49 [0.93-2.40]).

Were it a drug, PT would have been denied FDA approval which requires the treatment benefits to outweigh the potential harms. Yet, as has happened in other studies when serious potential hazards were ignored, any concerns about the safety of PT were dismissed by the investigators simply because the mortality difference between treatment groups was not statistically significant. Their conclusion that PT is both safe and effective prompted routine use of PT for ever smaller and more immature newborns in neonatal ICUs around the globe.

There is only one other large PT trial: our Neonatal Research Network (**NRN**) trial comparing aggressive PT (**AgPT**) and conservative PT (**ConPT**) (treatment regimens differing only in the total bilirubin [**TB**] thresholds for providing PT). While AgPT reduced neurodevelopmental impairment (**NDI**) in this trial it also significantly increased mortality among ≤ 750 g ventilator-treated infants (RR = 1.19; 95% CI (1.02-1.39)). This increase in mortality was found even though 80% of the ConPT group received PT, a factor that would diminish any difference between groups in any adverse effects of PT. Moreover, conservative Bayesian analyses (using a neutral prior probability) identified not only a 99% likelihood that AgPT increased deaths among ≤ 750 g ventilator-treated infants in the NRN trial but also a 92% likelihood that PT increased deaths among all extremely low birth weight (**ELBW**; ≤ 1000 g) infants in the Collaborative Trial. Both trials involved continuous (uninterrupted) administration of PT whenever the TB exceeded the treatment threshold.

Mechanisms by which continuous PT is likely to increase mortality. Immaturity, thin translucent skin, and a multitude of other problems may make extremely premature infants highly vulnerable to the photo-oxidative injury, lipid peroxidation, DNA damage, reduced cerebral and mesenteric blood flow, or other serious potential hazards of uninterrupted exposure to PT that have now been identified. Such hazards were not recognized when continuous PT was widely incorporated into neonatal care, and the survival rate of extremely premature infants (< 27 wks gestation or ≤ 750 g birth weight) was much lower than today.

PT was not subjected to the careful dose-finding studies that are ordinarily performed before therapies known to be toxic are introduced into the care of vulnerable patients. The history of neonatology is replete with therapies that proved to be hazardous in small premature infants at doses that are well tolerated in larger and more mature infants. The increased mortality associated with PT in the trials noted above may simply be due to an excessive “dose” of PT, particularly in the first few days after birth when the infants are most fragile, their skin is most translucent, and their **TBTB** levels are lowest. If so, an increase in mortality could be avoided by administering no more PT than needed to prevent unsafe TB levels.

Cycled PT as a method to avoid unnecessary PT likely to increase mortality among small, sick preterm infants. PT rapidly photoisomerizes bilirubin in the subcutaneous tissues and vasculature, and six trials of cycled PT have demonstrated that use of cycled PT reduces the total hours of PT and results in minimal or no increase in peak TB over that with continuous PT in term or moderately preterm infants. As described herein, we have conducted a 5-center randomized dose-finding trial of cycled PT involving 305 ELBW infants, the second greatest number of ELBW infants in any PT trial to date. PT was provided using the same treatment thresholds and irradiance as used for AgPT in the NRN trial, and PT was cycled using a simple automated timer. The findings support a PT regimen in which PT is provided for 15 min/h and increased only if the TB reached pre-specified levels. Among infants ≤ 750 g birth weight in this trial, PT was increased to 30 min/h if the TB was 8.0-9.9 mg/dL and to 60 min/h if the TB was ≥ 10 mg/dL. This regimen substantially reduced the total hrs of PT, particularly in the first 4 days after birth and resulted in a mean peak TB of 7.0 mg/dL, only 0.6 mg/dL higher than with continuous PT. For reasons noted below, this is considered to be a trivial difference in the TB of the two groups.

Cycled PT as a method to prevent unsafe TB levels that may cause NDI among infants in the proposed trial. Our dose-finding trial provided strong evidence that cycled PT regimen adequately controls TB:

1) Auditory brain-stem evoked responses (**BAERs**) were assessed, and no increase in the latency of wave V—a sensitive indicator of even transient bilirubin neurotoxicity—was found with cycled PT vs. continuous PT.

2) The peak TB level with cycled PT (7.0 mg/dL) was identical to that with continuous AgPT that reduced NDI in the NRN trial even though the total PT hrs were if anything lower than with ConPT (mean 33 vs. 35 hrs).

3) The peak TB level of 7.0 mg/dL is clearly lower than the lowest peak TB ever shown in a randomized trial to increase NDI (9.8 mg/dL for the ConPT in the NRN trial). In the Collaborative Trial, a mean peak TB of 9.9 among the infants who received no PT at all was not associated with NDI at 6 years age when compared to the infants treated with PT who had a mean peak TB of 6.8 mg/dL.

4) *At the same peak or even a somewhat higher TB value, the risk of bilirubin neurotoxicity and NDI may well be lower with cycled PT than with continuous PT.* Reasons include: a) as indicated above, cycled PT is expected to reduce life-threatening illnesses in the babies to be studied. The risk of NDI at a given TB is known to be higher among severely ill babies than healthier but otherwise similar infants; b) cycled PT may reduce the risk of brain injury to small premature infants by reducing a variety of known or suspected hazards of PT (e.g., DNA damage, blood flow alterations, hemolysis [that would not only increase bilirubin production but could cause bilirubin to be displaced from albumin]) and photo-oxidative injury and lipid peroxidation [that might compromise the blood brain barrier]; and c) administration of cycled PT using blue lights as in the dose-finding pilot and the proposed trial is likely to be more effective and to have a lower risk/benefit ratio in photoisomerizing bilirubin than white light PT that was used exclusively or commonly in the prior Collaborative and NRN trials and has often been used in clinical practice.

For the above reasons, careful scrutiny of the best available evidence indicates no reasonably foreseeable basis to conclude that patient risk would be increased by participation in this trial. If anything patient safety is likely to be greater and the risk of adverse outcomes lower in extremely premature infants treated with cycled PT. The proposed trial is thus a minimal-risk safety study in which extremely premature infants (≤ 750 g BW or < 27 wks GA) would be randomized to either AgPT, a continuous PT regimen commonly used in NRN centers, or to the ≥ 15 min cycled PT regimen supported by our dose-finding study. This pragmatic trial is designed to minimize the sample size, data collection, study duration, and cost in testing the hypotheses and providing the data needed to change clinical practice if appropriate in accordance with the tenets to 1) first do no harm and 2) use the lowest effective dose of a therapy to reduce the risk of known or unknown treatment hazards.

Hypotheses.

1. The ≥ 15 min/h cycled PT regimen will control peak TB (mean < 8.0 mg/dL) and reduce total PT h by $\geq 60\%$ in the 1st 4 d & $> 40\%$ in 1st 14 d after birth.

2. Cycled PT is likely to increase survival over that with continuous PT. As estimated in conservative Bayesian analyses (using a neutral prior probability), the (posterior) probability will be $\geq 70\%$ that cycled PT increases survival to discharge (1^o outcome).*

3. Cycled PT will not substantially increase (as indicated by a RR < 1.20) death or major neonatal morbidity: (severe ICH, PVL, BPD, NEC or spontaneous intestinal perforation, late onset sepsis, $\geq$ stage 3 ROP).

*The sample size to be studied (n=1700) affords 80% Bayesian power to identify the hypothesized posterior probability. It also affords $\geq 80\%$ power with an alpha error of 0.05 in frequentist analyses to identify increased survival to discharge (mortality RR ≤ 0.76), with a number needed to treat = 19).

Design Type. Pragmatic randomized clinical trial addressing patient safety

Exposure and Comparison. 1) The ≥ 15 min/h cycled PT regimen assessed in our dose-finding trial (with the same irradiance targets and TB indications as for AgPT); 2) **AgPT**, a continuous PT regimen commonly used in NRN centers and shown in the prior NRN PT trial to reduce both profound and severe NDI in ELBW infants.

Eligibility Criteria. Inborn infants ≤ 750 g BW or < 27 wks GA (by best obstetric estimate) without known hemolytic disease, major anomaly, overt nonbacterial infection or a very high likelihood of death (pH < 6.80 or persistent bradycardia with hypoxia for > 2 h) who can be enrolled by 12-36 h of age.

Primary Outcome. Survival to discharge.

Secondary Outcomes. Predischarge: Mean total h of PT; mean total irradiance hours; mean peak TB; mean TB; major neonatal morbidity (severe ICH, ventricular enlargement of cystic white matter disease, BPD, late onset sepsis, NEC or spontaneous intestinal perforation, or $\geq$ stage 3 ROP); the component pre-discharge morbidities; and patent ductus arteriosus treated with surgery or NSAIDS. Post-discharge: NDI and either death or NDI (assessed in generic follow-up of infants <27 wks gestation).

Section 2. Conflict of Interest Disclosures. None.

Section 3. Statement of Problem

Primary Hypothesis. Cycled PT is likely to increase survival over that with continuous PT. As estimated in conservative Bayesian analyses (using a neutral prior probability), the (posterior) probability will be $\geq 70\%$ that cycled PT ≥ 15 min/h increases survival to discharge (*1^o outcome*) above that with AgPT among extremely premature infants (≤ 750 g BW or <27 weeks GA).

As discussed in the sample size section, the trial will have $\geq 80\%$ power to assess this hypothesis in Bayesian analyses and to assess a 5.3% absolute increase in survival to discharge (from 78 to 83.3%) and a RR of death <0.76 (16.7%/22%) in frequentist analyses.

Secondary Hypotheses.

1. The ≥ 15 min/h cycled PT regimen will adequately control peak TB (mean <8.0 mg/dL and ≤ 1.5 mg/dL greater than with continuous PT) and reduce total PT h by $\geq 60\%$ in 1st 4 d & $>40\%$ in 1st 14 d after birth;
2. Cycled PT will not substantially increase (as indicated by a RR <1.20) death or major neonatal morbidity (severe ICH, PVL, BPD, late onset sepsis, NEC or spontaneous intestinal perforation, $\geq$ stage 3 ROP).

Background and Rationale. Important issues for the proposed trial include the following:

Why has continuous PT been assumed to be safe for extremely premature infants? PT was introduced into neonatal care almost 5 decades ago and extended to ever smaller and more immature infants under the assumption that uninterrupted exposure to bright lights is safe for all infants. Yet, extremely premature infants would normally develop in darkness within the uterus for 3-4 more months before birth, and their thin, translucent skin and immature defense mechanisms may make them quite vulnerable to photo-oxidative injury, lipid peroxidation, DNA damage, reduced cerebral and mesenteric blood flow, or other serious potential hazards of uninterrupted exposure to PT that have now been recognized.^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17} The risks of PT may include a small increase in the risks of cancer in later childhood.^{16,17,17a} Given all the factors that confound observational studies of PT administration to extremely premature infants¹⁸ and the possibility of important long term unknown hazards, randomized trials are crucial to verify that benefits of any PT regimen at least exceed the hazards in the neonatal period.

The only recent large trial of PT is the NRN trial comparing aggressive vs. conservative indications for PT. Both regimens involved uninterrupted exposure to PT. Led by Dr. Brenda Morris, a protégé of Dr. Tyson, this trial found that aggressive PT (AgPT) reduced NDI below that with conservative PT (ConPT) among infants ≤ 1000 g BW. However, preplanned frequentist analyses of the highest risk infant identified an increase in deaths with AgPT among 501-750 g ventilator-treated infants ($n=696$) (RR = 1.19; $p<0.05$ for a BW x treatment group interaction).¹⁹ Conservative Bayesian analyses identified a 97% probability that AgPT reduced NDI and a 99% probability that it reduced profound NDI but also a 99% probability that Ag PT increased mortality in this group. This probability was found even though 80% of the ConPT group received PT,²⁰ a factor that would be expected to reduce any adverse effects of PT identified in this trial.

The only trial comparing PT-treated infants with controls given no PT was the NICHD Collaborative PT trial ($n=1339$ LBW infants enrolled in the 1970s with survivors followed to school age). It is the only other large trial of PT, and it also provided worrisome evidence that PT increases mortality among LBW infants, particularly ELBW infants. While mortality was not significantly increased, the findings were compatible with a 32% increase in mortality among all LBW infants (RR for death with PT = 1.32; 95% confidence interval = 0.96-1.82) and a 49% increase among infants ≤ 1000 g BW (RR = 1.49 [0.93-2.40] with a 92% probability of increased deaths in Bayesian analyses.^{21,22} As expected, the PT group had fewer exchange transfusions than controls by the TB thresholds used at that time. For a number of reasons*, the current TB exchange thresholds are higher.²³ However, the investigators were surprised to find no evidence that PT reduced NDI, despite a

*The higher TB indications for exchange transfusion used now than during the Collaborative Trial can be justified by 1) the absence of discernible neurologic or cognitive deficits attributable to bilirubin neurotoxicity among control infants in the Collaborative Trial, and 2) the multiple factors likely to reduce the true risk of bilirubin neurotoxicity at a given measured peak TB level today than during or before the Collaborative Trial. These factors include a) more frequent measurement of TB (a factor that would increase the measured peak TB at a given true peak TB), b) the higher proportion of the measured TB level due to photoisomers after even a brief exposure to PT (K Mrehil et al, 2010). These photoisomers have a structure considered unlikely to be neurotoxic; c) the virtual elimination of severe hemolytic disease due to Rh incompatibility; d) the removal of benzyl alcohol from IV fluids. In some studies, benzyl alcohol was associated with a markedly increased risk of kernicterus (D.S. Jardine and K. Rogers, 1989). Higher TB indications for exchange transfusion today than in the past are also appropriate because these procedures are now rarely performed, and physician inexperience is likely to increase the risk/benefit ratio at a given TB level.

substantially lower mean peak TB among PT treated infants than among controls (6.4. vs. 9.9 mg/dL). The PT and control groups had an almost identical percent of infants with deafness (the primary outcome) (1.8 vs. 1.9%), cerebral palsy (5.8 vs. 5.9%), and clumsiness or hypotonia (11.1 vs. 11.4%). No infant with athetosis was identified, and PT was not shown to increase cognitive test scores.²⁴

Had the safety and effectiveness of PT been evaluated as a drug, the FDA would not have approved it for clinical use based on findings in this large trial compatible with a substantial increase in mortality with no reduction in NDI. Yet, despite the quite worrisome mortality data and the lack of discernible benefit for the primary or other neurodevelopmental outcomes, the investigators did not call for further study or even caution in interpreting the results. Instead they concluded that “Phototherapy effectively controlled hyperbilirubinemia without evidence of adverse outcomes....We believe that PT is safe and effective.”

This conclusion by prominent investigators in a multicenter NIH-funded trial promoted widespread use of continuous PT for even the smallest and most immature infants. Commenting on the same data in 1986, Dr. Ronald Poland (who later became a NRN Chairman) argued that the safest assumption was that PT might increase mortality in LBW infants.²⁵ His concern was dismissed by the investigators²⁶ who like many prior investigators ignored a serious potential hazard because the difference between treatment groups was not statistically significant. As discussed below, this issue is not only of fundamental importance in justifying the proposed trial but also in interpreting trials of any intervention in patients of any age.^{27,28}

How should sizable but statistically non-significant differences for treatment hazards be interpreted? Should the p value for statistical significance be higher for treatment hazards than treatment benefits? In addressing these questions, it may help to first consider what evidence from clinical trials would most clearly justify a conclusion that a therapy should *not* be used. To illustrate, suppose a literature search were performed to identify well-performed randomized trials that identified 1) no evidence of a clinically important benefit for the 1^o outcome or outcomes of equal or greater importance, 0 and 2) findings compatible with a major increase in deaths. Suppose also that trials meeting these criteria included ones that identified the following values for the RR (95% CI) for death for the treatment group vs. the control group:

1. RR = 1.24 (0.69 - 2.25)
2. RR = 1.32 (0.96 - 1.82)
3. RR = 1.37 (0.92 - 2.04)
4. RR = 1.49 (0.93 - 2.40)

While none of these results were significant at a $p < 0.05$, they are fully compatible with a 24-49% increase in mortality with the 95% confidence intervals compatible with a more than two fold increase in deaths in 3 of the 4 trials. In the absence of other trials supporting these therapies, all these results might well justify a recommendation not to use the therapy for patients meeting the eligibility criteria for this trial. The basis for such a recommendation would be particularly strong for the above result 4 that has both the highest RR (1.49) and the highest upper limit of the 95% confidence interval (2.40).

Result 4 above was that for PT for extremely LBW infants in the Collaborative Trial, a result strangely accompanied by a conclusion that PT was safe for these infants. Result 2 was that for LBW infants in that trial. Result 1—the result with the lowest RR and lowest bound of the 95% confidence interval—is the weakest evidence of an increase in deaths. Yet it was the interim result for the deeper cooling group in the NRN Optimizing Cooling trial,²⁹ a result considered to provide such strong evidence of harm that enrollment in this trial was stopped early with no further patients allowed to receive either deeper cooling or longer cooling (result 3). This decision was made despite the absence of any data for the primary outcome (death or NDI at 2 years).

This decision in the Optimizing Cooling Trial reflects the greater concern that Data Safety Monitoring Committees generally accord to evidence of treatment hazards than to treatment benefits in deciding whether to stop trials based on interim results. To assure that the Type 1 error does not exceed 0.05 despite multiple interim analyses of the primary outcome, stopping guidelines to discontinue a trial early for treatment benefit often require a $p < 0.01$ or even lower in the early interim analyses. However, stopping a trial for a serious treatment hazard at a $p > 0.05$ (including a $p = 0.14$ in the Optimizing Cooling trial) can be viewed as prudent and appropriate because of 1) the general ethical tenet: “First Do No Harm” and the willingness to accept a greater likelihood of missing a true benefit in order to reduce the likelihood of missing a serious hazard; 2) the greater effort generally devoted in trials to identifying treatment benefits than hazards, 3) the low proportion of well investigated interventions that prove to be a major advance and the high proportion that turn out to have less benefit and/or greater hazard than originally hypothesized or reported.^{30,31}

PT is administered to almost all ELBW infants. Given the findings of the only two large PT trials, including a 92% probability that PT increased deaths among infants in the Collaborative Trial and a 99% probability that AgPT increased deaths among ventilated ≤ 750 g infants in the NRN PT trial, high priority should be given to identifying and testing ways to effectively lower TB levels without risking an increased mortality among the infants we propose to study (infants ≤ 750 g BW or < 27 weeks GA).

What rationale and evidence supports cycled PT for extremely premature infants? The photons delivered by PT are analogous to the molecules of a drug, irradiance (photons/unit time) is analogous to dose rate, and the total number of photons provided is analogous to the drug dose. When delivered to a 3 kg infant, PT provides $\sim 2 \times 10^{23}$ total photons in 8 hours (substantially greater than the total number of molecules of drug in administering a medication like ampicillin.) As indicated by Lamola,^{31a} the analogy to administration of a medication fails in only one important regard that may cause the hazards of PT to be underestimated: light absorption leads to heat deposition with potential adverse effects.

Continuous administration of PT may increase the mortality of extremely premature infants simply because uninterrupted exposure may result in a “dose” of PT that is substantially higher than needed. In 1972 Lucey noted that “intermittent light therapy is effective” and that “the originally arbitrarily chosen light conditions often supply more light than is needed.”³² Bilirubin is photoisomerized within nanoseconds after exposure to light, and six trials in larger infants as well as our dose-finding study in ELBW infants (see below) have found that cycled PT results in minimal or no increase in TB levels compared to continuous PT.^{33,34,35,36,37,38} As little as 15 minutes of PT every 75 minutes have been assessed and found to be effective in moderately preterm infants.³⁵ The total minutes of cycled PT needed per h to control TB may well be lower in extremely premature infants than in other infants due to their relatively high skin blood flow, increased surface area/mass ratio, translucent skin and subcutaneous tissue, and photoisomerization of bilirubin within their skin and vascular tree. At the same total exposure to PT, use of cycled PT for limited periods (e.g. 15 min) each hr would effectively photoisomerize most new bilirubin produced in the prior hr and would be expected to result in a lower peak TB than would longer but less frequent periods of PT (e.g., 6 h of PT given once every 24 h).

Studies of cycled PT were apparently inhibited because of a tissue culture study performed 4 decades ago reporting DNA damage.³⁹ Later in-vivo studies verified that PT does result in DNA damage but that it is usually transient and related to total exposure to PT.^{10a,10b,40,41} Such findings should not discourage trials like we propose to determine whether use of cycled PT to reduce to the total duration or “dose” of PT would reduce the mortality of extremely premature infants.

Dose-finding studies are routinely performed for predictably toxic therapies like those to treat cancer. However, continuous administration of PT was assumed to be quite safe and has been widely used without dose-finding studies. We have conducted a dose-finding study using cycled PT in 305 ELBW infants in 5 centers including 3 Network centers (UT Houston, Stanford, UAB, and UT Southwestern). Infants have been stratified by center and BW group before randomization. This dose-finding trial was designed to avoid the limitations of most dose-finding studies which have usually been small, single center, nonrandomized studies performed without specific hypotheses. Moreover, the doses recommended based on typical dose-finding studies have been based on pharmacokinetic assessments and measures of outcomes or toxicity that are relatively crude surrogate outcome measures.

How does our dose-finding study of cycled PT inform the proposed trial? As indicated below, this trial was designed to maximize its value in designing a larger trial to determine whether cycled PT should be routinely used for extremely premature infants.

Design. The exclusion criteria, age and TB thresholds for starting PT, irradiance range, and exchange transfusion criteria have been the same as for AgPT in the NRN PT trial. Simple, inexpensive timers have been used to automatically cycle PT. As explained below, ELBW infants were randomized into 3 treatment groups: 1) Continuous PT; 2) Cycled PT given for ≥ 30 min of PT per h; 3) Cycled PT given for ≥ 15 min of PT per h. To administer no more PT than needed to control the TB of individual infants, we have started with the minimum duration noted for cycled PT group but increased PT if the TB rises to the values shown in the Table below. Once TB levels fall sufficiently, we have resumed giving PT for the minimum time for each cycled PT group.

Table 1. TB values (mg/dL) used to adjust duration of PT			
BW and PT treatment group	PT given for minimum min/h	PT increased to 30 min/h	PT increased to 60 min/h
BW 401-750g ≥15 min/h	5-7.9	8-9.9	≥10
≥ 30 min/h	5-7.9	—	≥8
BW 751-1000g ≥ 15 min/h	5-9.9	10-11.9	≥12
≥ 30 min/h	5-9.9		≥10

As indicated below, the duration of PT has been increased for only a minority of cycled-PT infants. Irradiance is started at 22 $\mu\text{W}/\text{cm}^2/\text{nm}$. If needed, irradiance is increased to 33 at a TB (mg/dL) of 10 for infants 401-750 g BW and 12 for infants 751-1000 g BW and to 40 at a TB of ≥ 13 for 8h for 401-750 g infants and ≥ 15 for 8h for 751-100 g infants. While the NRN trial did not require use of blue LED PT lamps, these lamps have been uniformly used in the dose-finding study in an effort to maximize the effectiveness of PT and reduce unnecessary irradiance exposure and increase the safety of PT.^{15,42}

Hypotheses of dose-finding trial. We hypothesized 1) a small difference (<1.5 mg/dL) in the peak TB between the three treatment groups; 2) a mean peak TB <8.0 mg/dL in each group; 3) a similar latency of wave V of the brain-stem auditory evoked responses (**BAER**)--a sensitive indicator of even transient bilirubin neurotoxicity^{43,44,45,46}--in each group.

Findings. The treatment groups have similar baseline characteristics (Table 2 showing the most recent analyses). The smaller n in the 30 minute cycled PT group reflects a decision to drop that group after interim analyses indicated that the ≥ 15 min cycled PT group resulted in comparable TB levels with less PT than in the ≥ 30 min cycled PT group.

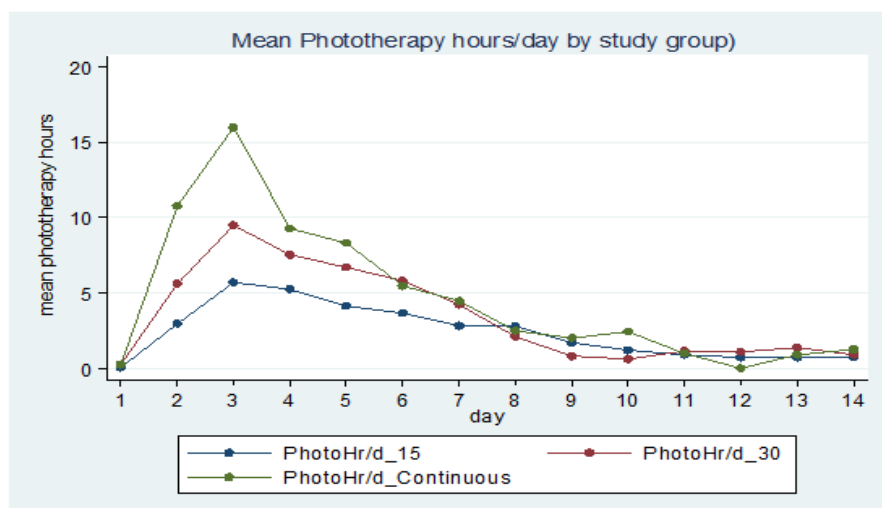
Table 2: Baseline Characteristics			
	≥ 15 Min Cycled PT n=121	≥ 30 Min Cycled PT n=34	Continuous PT n=118
Gestational Age – wks (mean $\pm$ SD)	26.2 $\pm$ 1.8	26.0 $\pm$ 1.3	26.1 $\pm$ 1.8
Birthweight – g (mean $\pm$ SD)	760 $\pm$ 149	784 $\pm$ 162	736 $\pm$ 147
Male sex – n (%)	55 (45)	10 (29)	56(47)
Antenatal steroids – n (%)	105 (87)	32 (94)	111 (94)
Risk Strata – n (%)			
High risk	54 (45)	13 (38)	53 (45)
Low risk	67 (55)	21 (62)	65 (55)
Cesarean delivery – n (%)	93 (78)	24 (71)	99 (84)
Apgar score at 5 min <5 – n (%)	24 (20)	4 (12)	22 (19)
Hematocrit at <12 hr of age (mean $\pm$ SD)	42.6 $\pm$ 7.1	41.1 $\pm$ 6.9	43.8 $\pm$ 6.8

Baseline Total Bilirubin mg/dl	3.6 ± 1.0	3.2 ± 0.7	3.4 ± 1.0
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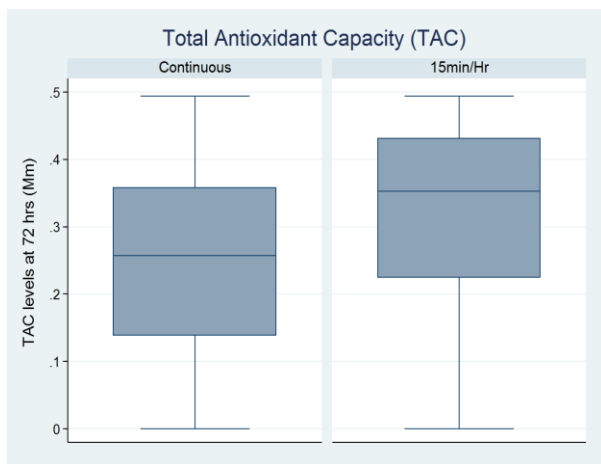
The findings for peak TB and use of PT (Table 3) in all analyses to date provide strong support for our hypotheses with the mean peak TB of the ≥ 15 Min cycled PT being 7.0 mg/dL, only 0.7 mg/dL less than that for continuous PT.

Table 3	≥ 15 Min Cycled PT n=121	≥ 30 Min Cycled PT n=34	Continuous PT n=118
Peak TB, mg/dl mean $\pm$ SD	7.0 $\pm$ 1.7	6.5 $\pm$ 1.1	6.3 $\pm$ 1.2
Peak TB minus baseline TB, mg/dL, Mean $\pm$ SD	3.5 $\pm$ 1.6	3.3 $\pm$ 1.2	2.9 $\pm$ 1.4
Duration of phototherapy, hr mean $\pm$ SD	32.8 $\pm$ 18.5	48 $\pm$ 26.3	72.8 $\pm$ 35.1
Need to intensify phototherapy, n (%)	22 (18)	2 (6)	1 (1)
Exchange transfusions, n	0 (0)	0 (0)	0 (0)

Evaluation of the total h of PT each postnatal day in each of the 3 groups provides further evidence of the safety of cycled PT. As shown in the Figure, the greatest decrease in PT with cycled PT occurred in the first 4 days after birth before TB peaked and when the skin is least cornified, the infants are likely to be sickest, and the risk/benefit ratio of continuous PT would presumably be most unfavorable. Findings were similar in the smallest & most immature infants.



Whether this reduction in phototherapy would result in antioxidant depletion is uncertain. Total antioxidant capacity (TAC)^{46a-46d} was measured at Stanford under the direction of Drs. Ron Wong and David Stevenson in 32 patients in this dose-finding study. The point estimate for the difference in TAC levels favored the 15 minute group: 0.24 vs. 0.35 mm. As expected with small numbers, the difference was not significant (p=0.29). However, the box plot below suggests that antioxidant depletion could be a mechanism mediating PT toxicity.¹



Wave V latencies of the BAERs are shown in Table 4 below. The data have provided no evidence of bilirubin neurotoxicity in unadjusted analyses or in analyses adjusted for GA and risk strata.

	≥15 Min Cycled PT n=37	≥30 Min Cycled PT n=20	Continuous PT n=33
Wave V latency — ms mean ± SD	7.4 ± 0.5	7.4 ± 0.4	7.4 ± 0.5
Adjusted** mean difference in wave V latency (95% CI)	0.13 (-0.07, 0.33)	0.03 (-0.19, 0.26)	Reference

The dose-finding study was not powered to identify differences in mortality. However, the results to date for infants who have been discharged from the NICU are not incompatible with the mortality difference hypothesized for the proposed trial. Their overall mortality is 11/111 (9.9%) with ≥15 min regimen vs. 13/110 (11.8%) with continuous PT.

Relation of findings to prior PT trials. The above indicates that the ≥15 min/h cycled PT regimen results in:

1) a mean peak TB (7.0 mg/dL) that is considerably lower than the lowest value associated with NDI in any prior trial (9.8 gm/dL in the ConPT group in the NRN trial). As noted above the mean peak TB of 9.9 mg/dL in control infants who did not receive PT in the Collaborative PT trial was not found to result in more neurological or cognitive deficits than among similar infants randomized to receive PT.

2) a mean peak TB level identical to that in the AgPT group of NRN trial (7.0 mg/dL) which resulted in reduction in the rate of NDI, particularly profound NDI, among ELBW infants, relative to that with ConPT. The mean peak value for cycled PT was only 0.7 mg/dL higher than for continuous PT in our dose-finding study, and no evidence of bilirubin neurotoxicity was identified in the BAERs assessed. *For reasons indicated above and summarized in the Synopsis, the risk of brain injury at the same or even a somewhat higher TB may well be less with cycled PT than with continuous PT.*

3) a mean duration of PT (32 h) that is (a) less than half that with continuous PT in both our dose-finding study (65 h) or in the AgPT group in the NRN trial (88 h) and (b) a bit less than that with ConPT in the NRN trial (35 h), a duration associated with a lower mortality than with AgPT. Moreover, as emphasized above, PT administration with cycled regimens was specially reduced during the first 4 postnatal days when the risk/benefit ratio of PT may be least favorable.

Implications of current evidence regarding continuous and cycled PT. These findings strongly support the trial we propose and suggest that the ≥15 min/h cycled PT regimen would prevent bilirubin neurotoxicity as effectively as AgPT without risking a higher mortality than with ConPT among extremely premature infants.

Central issues in the design and analysis of the proposed trial.

1. What PT regimens should be compared? The exposure to or “dose” of PT received by extremely premature infants might be limited not by using cycled PT but by using more conservative indications for PT or reducing the irradiance during PT. However, the Collaborative Trial involved a much lower irradiance during PT than is used today and provided no evidence that reduced irradiance would lower mortality. Moreover, use of reduced irradiance was not associated with an improvement in NDI. Use of more conservative indications for PT were tested in the NRN PT trial, and while this approach may reduce mortality, it increased NDI relative to PT using aggressive indications. Thus, use of cycled PT would seem to be the most promising method to reduce exposure to PT while minimizing the risk of NDI. Given the data provided above, we propose that the specific cycled PT regimen used for the intervention group be the ≥ 15 min/h cycled PT regimen.

Some NRN PIs suggested that in each center the comparison arm should be whatever the usual care is in this center. However this approach is unsuitable for the following reasons: 1) In some NRN centers, it would involve non-standardized regimens with different attendings using different regimens that would be difficult to describe or monitor and that might change during the trial; 2) Regimens other than AgPT or ConPT are based only on biological plausibility, and none have been shown in clinical trials to reduce NDI or other adverse outcomes. Regimens intermediate between AgPT and ConPT could result in worse outcomes than with either, possibly resulting in NDI rates no better than with ConPT and mortality rates no better than with AgPT; 3) It would be unclear what hypotheses would be tested or what effect size should be hypothesized; and 4) Differences within and between centers might well result in significant heterogeneity in treatment and reduce the likelihood of obtaining a clear answer to any meaningful question.

The reasons we propose that the comparison arm be the AgPT regimen tested in the NRN trial include:

A. AgPT is the only PT regimen shown to reduce NDI in any trial. Moreover, in the NRN trial it substantially reduced profound NDI (Bayley II Mental Developmental Index ≤ 50 or a Palisano gross motor function score of 5) with a RR = 0.68 [0.52-0.89] below that with ConPT. Few if any perinatal interventions have been shown to have such an effect.

B. Because AgPT was the comparison arm in the dose-finding study, we can be most confident in hypothesizing the effects of cycled PT regimen relative to those with AgPT

C. Our survey of NRN sites indicates that the aggressive PT regimen is most commonly used across NRN centers.[†] Seven centers use only AgPT. Other centers allow attending neonatologists to have discretion in use of PT and had little data regarding their actual practices. No response indicated that AgPT could not be used. If ConPT is used at all, the responses suggest that it may be used in only one center.

2. What population should be studied? Cycled PT might be preferable to continuous PT for the routine care of all ELBW or even larger infants. To reduce its cost and sample size, the proposed study is focused on extremely premature infants, the subgroup group likely to be most vulnerable to any hazards of uninterrupted exposure to bright light. Should our hypotheses be confirmed, our findings in combination with those of the other studies noted above would likely promote routine use of cycled PT in treating ELBW infants and perhaps investigation of cycled PT for larger infants.

3. What should be the primary outcome? Based largely on the prior two large trials of continuous PT, we hypothesize that cycled PT increases survival to discharge (reduces pre-discharge mortality). For the following reasons, we haven't hypothesized an effect of cycled PT on NDI and don't propose that the primary outcome be a composite primary outcome of death or NDI.

A. As noted above, there is no evidence that NDI would be increased at peak TB levels close to those with cycled PT in our dose-finding trial to date (7.0 mg/dL). With the wave V latency of ABRs being a sensitive sign of even transient bilirubin neurotoxicity, the BAER findings in our dose-finding study are reassuring.

[†] The indications for starting/stopping PT in clinical practice were not standardized and somewhat uncertain in a number of NRN centers. However, the survey responses indicated that the AgPT has been uniformly used in 7 NRN centers (Brown, Cincinnati, Duke/UNC, Houston, Iowa, New Mexico, Stanford) and that the practices were either “generally aggressive” or close to AgPT in an additional 2 centers (Alabama, Case). Responses from other centers (e.g., CHOP, Emory, Rochester, Utah) indicated variation in clinical practice that apparently includes both AgPT as well as somewhat more conservative practice. The guidelines for one center (Emory) were broad enough to potentially include use of PT as conservative as the ConPT regimen in the NRN trial. No center provided a response indicating that AgPT could not be used.

B. Concerns that NDI that the minimal increase in peak TB with cycled PT lack biologic plausibility as well as an evidence base. Any increase in risk of NDI from a small increase in TB might well be more than offset by a decrease in a) any PT-induced hemolysis or life threatening illnesses that increase the risk of bilirubin neurotoxicity at a given TB, b) administration of medications that may displace bilirubin from albumin in treating these illnesses, c) lipolysis or other adverse effects of PT that may compromise the blood brain barrier, or d) other adverse effects that would increase the risk of bilirubin neurotoxicity at a given TB.

C. If cycled PT has no effect on NDI among survivors, the sample size, study duration, and study costs to test the effect of cycled PT on mortality will be considerably less than to test the effect on the composite outcome of mortality or NDI. The greater sample size reflects the increase in signal to noise ratio when a treatment-unresponsive outcome (NDI) is combined with a treatment responsive outcome (mortality).

D. With survival to discharge as the primary outcome, the primary manuscript can be published without waiting for two-year follow-up assessments.

As noted above, survival without NDI can be published in a later report of generic follow-up for infants <27 wks gestation. If additional funding is provided, infants >27wks who weighed ≤ 750 g at birth can be included. (If so, the confidence interval for the difference between groups is expected to be $\pm 4\%$).

4. What secondary outcomes should be assessed? These would include major neonatal morbidities evaluated using the same definitions and assessment methods in evaluating them as secondary outcomes in the NRN PT trial. We will also include patent ductus arteriosus treated with surgery or NSAIDS, an outcome possibly increased by PT exposure.^{46e} NDI, the components of NDI, and survival without NDI will be assessed in generic follow-up of infants <27 weeks gestation. If funding is obtained, ELBW infants who are ≥ 27 weeks would also be assessed.

5. What evidence should be required to alter recommendations for PT use in clinical practice? As indicated above, the current relevant evidence includes 1) a 92% probability identified from the Collaborative Trial that PT increases deaths among infants ≤ 1000 g BW; 2) the 99% probability identified in analyses of the NRN trial that aggressive use of PT increases deaths among ventilator treated infants ≤ 750 g BW; 3) a variety of demonstrated or potential adverse effects that may contribute to an increased mortality¹⁻¹⁷ and 4) the findings in our dose-finding trial and 6 prior trials in large infants that total PT exposure can be substantially reduced with minimal increase in peak TB.

Considering this evidence, the burden of proof should arguably rest on those who would now recommend routine use of continuous PT to demonstrate that it does not increase mortality and is necessary to adequately control TB. Such a requirement would be justified by: 1) the implausibility that bright light should be assumed to have no serious hazards for translucent, immature, fragile and often quite sick infants; 2) the accruing evidence of a variety of PT hazards that could contribute to an increase in mortality or other adverse effects¹⁻¹⁷; and 3) two standard clinical tenets: A) *First, do no harm* and B) *Use the lowest effective treatment dose to reduce risk of unknown as well as known hazards.*

The second of these two tenets is based on the fact that virtually all if not all therapies have hazards and that the higher the dose, the more common and more serious the hazards—known and unknown—are likely to be. Exposure to bright light is a potent stimulus in early life in many species^{47,48,49,50} and might have major as yet unidentified hazards in later childhood or even adult life. The evidence supporting cycled PT for ELBW infants is already of similar or better quality than that supporting many current “standard” therapies, including the antibiotic regimens for treating neonatal sepsis or meningitis. These regimens have generally been based on pharmacokinetics, blood or CSF levels, and the interval after starting treatment that blood or CSF cultures are no longer positive. The recommended regimens were generally adopted without demonstrating a favorable effect on long-term outcomes compared to potential alternative treatment regimens.

For these kinds of reasons, a change in clinical practice would be justified if the results indicate a high likelihood that cycled PT increases survival to discharge with no evidence that it appreciably increases the composite outcome of mortality or major morbidity in the neonatal period or at follow-up. This rationale is the basis for the hypotheses we propose to test.

Section 4 Methods.

4.1 Population and Inclusion/Exclusion Criteria: While infants who are ≤ 750 g BW but ≥ 27 wks by best obstetric estimate are not routinely included in NRN follow-up, we propose to include them in the trial because 1) GA estimates are often in error for extremely preterm infants^{51,52,53,54} and their true GA may well be < 27 weeks; 2) As shown in developing the NRN estimator, BW is no less important than GA in predicting outcome. (A 100 g difference in BW—which is no more than the increase in BW/week before 28 wks—was found to have a GA equivalent effect of 1.04 wks for death and 1.16 wks for death or NDI.⁵⁵); 3) As indicated above, the best evidence relating PT to the mortality of extremely premature infants is based on BW rather than GA; 4) Many, if not all, NRN centers now enroll all ≤ 750 g BW survivors, irrespective of GA, in their follow-up program.

4.1.1 Inclusion Criteria at randomization (enrollment)

1. Infants is inborn
2. Infant is ≤ 750 grams at birth or < 27 weeks gestation at birth by best OB estimate
3. Infant is 12-36 hours of age.

4.1.2 Exclusion Criteria

1. Unable to enroll by 36 hours of age
2. Previous phototherapy
3. Known or strongly suspected hemolytic disease
4. TB reported as ≥ 6.0 mg/dL before 12 hours age or as ≥ 7.0 mg/dL if not already enrolled (exclusion criteria to help avoid inclusion of infants most likely to develop high TB levels due to unrecognized hemolytic disease or other reasons.)
5. Major anomaly
6. Overt nonbacterial infection
7. Infant is likely to expire soon: Limiting or withdrawal of intensive care is being recommended to the parents, the parents are requesting withdrawal of care, or the pH is < 6.80 or persistent bradycardia with hypoxemia for > 2 h.

If there is uncertainty whether any of the above exclusion criteria are present, rely upon the judgment of the responsible neonatologist. The proportion of all eligible infants who are enrolled will be calculated based on the above criteria. In this population of inborn infants inability to enroll infants by 36 hours is not considered an exclusion criterion but a limitation of participating centers ability to enroll eligible infants.

4.2.2 Consent, Enrollment and Randomization. Consent may be obtained at any time before 36 h age using an IRB-approved consent procedure and consent form. This trial is proposed as a study to increase patient safety, and it is possible that it may be approved by the IRB in some centers for modification of consent.

Regardless of when consent is obtained, infants will not be considered enrolled before randomization. Randomization (enrollment) cannot occur prior to 12 hours or after 36 hours from birth. To the extent reasonably feasible randomization (when enrollment occurs) should be as close to 24 h age (as was done in the dose-finding trial and was close to the median age in the NRN trial) for infants whose TB is unknown or is identified as < 5.0 mg/dL. Eligible infants who have a TB of ≥ 5 between 12 and 36 h should be randomized and have PT started as quickly as possible.

Randomization will be stratified by center, mechanical ventilation at enrollment (yes; no), and BW (≤ 650 g; > 650 g) to help avoid important chance differences between treatment groups and facilitate analyses of interaction of these variables with treatment group. Twins or other multiples will be randomized to the same treatment. Infants will be randomized 1:1 to each treatment group in each stratum using a variable block size.

4.2.3 Intervention and Comparison Therapies and Study Procedures.

Treatment groups. Infants will be randomized to either:

1) The ≥ 15 min/h cycled PT regimen assessed in our dose-finding trial, a regimen that uses the same irradiance targets and TB indications as for AgPT but minimizes the PT exposure of individual infants increasing PT from 15 min/hr to 30 or 60 min/hr if needed to control the TB. As for infants in the dose-finding study, PT will be given 30 min/h if the TB is 8.0-9.9 mg/dL and 60 min/h if the TB is ≥ 10 mg/dL. (The same thresholds will be used for infants with direct hyperbilirubinemia; however, the attending neonatologist has the option to remove the infant from the treatment protocol [although the infant will be analyzed as randomized in the intention-to-treat analyses]). PT will be cycled using a simple timer selected based on its accuracy and ease of use that can be plugged directly into a wall outlet or appropriate power strip.

2) AgPT, the continuous PT regimen that is commonly used in NRN centers and that was found in the prior NRN PT trial to significantly reduce both profound and less severe neurodevelopmental impairment (**NDI**) in ELBW infants.

Type of PT Lamp. Narrow spectrum, blue, light-emitting diode (**LED**) lights^{15,40} will be used in both treatment groups because these lights are likely to have a better risk to benefit ratio than PT using a broader light spectrum and because they were used in our dose-finding trial. While the specific model of blue LED lamp can vary between hospitals, the same model should be used in the same hospital for all enrolled infants to avoid potential differences between groups in their treatment as well to help assure that the appropriate model-specific radiometer is used to assess irradiance in all infants. Biliblankets may be used if and when the TB is ≥ 10 mg/dL.

Indications for starting or resuming PT. PT will be started as close as reasonably feasible to 24 hr from birth, unless the TB is found to ≥ 5.0 mg/dL between 12 and 36 hr, which should prompt PT to be started for study babies as soon as possible. As shown in Table 5 below, PT will be continued or restarted whenever a TB (mg/dL) is ≥ 5.0 mg/dL through day 14. Whenever PT is administered, it will be given for at least 24 hours. (During that ≥ 24 hour period, the duration of cycled PT per hour and if needed the irradiance should be adjusted according to changes in the TB)

PT schedule and irradiance. The PT lamp position will need to be adjusted to meet the routine irradiance ($\mu\text{W}/\text{cm}^2/\text{nm}$) goal of 22 at the umbilicus (as in the NRN trial). The irradiance goal in both groups will be increased from 22 to 33 at a TB of 10-13 and to 40 at a TB ≥ 13 (very unlikely). *It is essential to use the model-specific radiometer to obtain meaningful irradiance values.* Providing the irradiance goal can be achieved, it is preferable to use a single PT lamp. (Whenever more than one lamp is used for the same infant, they must be the same model so that irradiance can be measured in a meaningful and accurate way.)

Table 5. PT administration from randomization ^a through postnatal day 14

TB (mg/dL)	Cycled PT (min/h)	Continuous PT (min/h)	Irradiance ($\mu\text{W}/\text{cm}^2/\text{nm}$) Both groups
<5.0^a	0	0	NA
5.0-7.9	15	60	22
8.0-9.9	30	60	22
10.0-12.9	60	60	33
>13.0^b	60	60	40

^a During the 1st 24 h after randomization, administer PT for 24 hr (even if all TBs during this 24 h period are <5.0; in this circumstance administer PT as if the TBs were 5.0-7.9 in Table 5). From 24 h after randomization through postnatal day 14, administer PT whenever the prior TB is ≥ 5.0 and discontinue it only when PT has been administered for at least 24 hours and the TB is <5.0 mg/dL. While the PT is being administered adjust it as in Table 5 according to the infant's most recent TB.

^b Perform exchange transfusion at TB ≥ 13.0 mg/dL after 8 h of PT given 60 min/h at irradiance of 40 unless responsible neonatologist considers the hazards to outweigh the benefits of exchange transfusion for the infant.

Exchange transfusions. Unless the attending neonatologist considers the infant unable to tolerate the procedure, an exchange transfusion will be performed for a TB ≥ 13 after 8 h of such intensified PT (the indication also used in the NRN PT trial).

TB determinations. As in most NICUs and in the prior NRN trial, TB will be recorded daily or more often in the 1st week and once daily in the 2nd week if the last TB was ≥ 5.0 or the infant was treated with PT in the prior

24 h. Less frequent TBs may result in overuse of PT or failure to promptly identify an unexpected TB increase. The method to measure total bilirubin (TB) should be the method regularly used in each NICU to manage phototherapy in very premature newborns. The same TB thresholds will be used for infants with direct hyperbilirubinemia (≥ 2 mg/dL); however, the attending neonatologist has the option to adjust the PT treatment protocol without evoking a protocol deviation or violation.

Other aspects of care. Other than as specified above, the treatment of the infants including umbilical cord clamping time, feedings, fluid administration, and transfusions will be at the discretion of the clinical staff.

Coordinator in-service and monitoring responsibilities. In initiating the study, NRN research nurses will in-service NICU personnel and place appropriate information at the bedside (including phone numbers to call study staff if questions or problems arise) of all study babies. Each center will establish procedures to assure data reliability and access, preferably in the EMR. As appropriate for a pragmatic trial, we would not require study nurses to go to the bedside each day to verify appropriate use of cycled PT and data entry throughout the study. Instead, we propose that they make daily visits to the bedside during the first study week for the first 14 infants enrolled in their center. In the second week for these patients, and for both the first and second week in subsequent patients, routine monitoring will be via the EMR, with phone calls and bedside visits as needed. The research nurses should discuss any recurring problems with data reliability or treatment compliance with the center PI who would then be responsible for correcting these problems.

4.2.4 Blinding/Masking. Blinding of parents and caregivers will not be feasible. However, the laboratory personnel who perform TB determinations will be unaware of treatment group. The personnel who assess neurodevelopmental outcomes at 2 years will be blinded to treatment group.

4.2.5 Confounding. No confounders are expected in this randomized trial. If despite randomization with stratification for center, mechanical ventilation at enrollment (yes; no), and BW (≤ 650 g; >650 g), any important differences between treatment groups occur in baseline variables related to outcome, secondary analyses will be performed controlling for these factors.

4.2.6 Effect modifiers and mediators. Potential effect modifiers include the above stratification variables, GA, chest compression and/or epinephrine in the delivery room, ventilation and FiO_2 at 24, sepsis at or before enrollment, sex, and ethnicity/race. In prior analyses of the NRN PT trial, these and other variables that may influence risk of bilirubin neurotoxicity were assessed singly and in combination and added little beyond BW stratum and mechanical ventilation at 24 hours. Because a three-way interaction was identified in the NRN trial between BW stratum, mechanical ventilation at 24 h, and treatment group,¹⁹ we would hypothesize such an interaction in the proposed study (although the population will be somewhat different and the use of CPAP has likely reduced the use of mechanical ventilation at 24 h). No other effect modifiers are hypothesized; the identification of other effect modifiers in the analyses should be treated as hypothesis generating. If a difference in mortality is identified, exploratory analyses will be performed to assess potential mediators (e.g. intracranial hemorrhage, sepsis, necrotizing enterocolitis, or chronic lung disease).

4.2.7 Primary Outcome. Survival to discharge. For infants transferred to another hospital from NRN centers, this outcome is to be assessed whenever feasible as discharge to home rather than from the NRN center.

4.2.8 Secondary Outcomes (as recorded for items in the generic database shown in the footnotes below).

Predischarge: Mean total h of PT in 1st 4 d and 1st 14 days after birth, mean total irradiance hrs; mean of highest TB value measured at any time; mean peak TB of TB measurements nearest 7 AM (morning labs) (included to avoid a potential bias resulting from more TB measurements in the cycled PT group); mean TB; major neonatal morbidity (severe ICH,^a ventricular enlargement of cystic white matter disease,^b BPD,^c late onset sepsis, NEC or spontaneous intestinal perforation,^d or $\geq$ stage 3 ROP^e); the component pre-discharge morbidities, and patent ductus arteriosus treated with surgery or NSAIDs.

^a as recorded for the sonogram with the most severe finding on the NGO3 item D4d Blood/echodensity in the ventricle: Yes to either Right or Left or NGO2 item 4 g Blood/echodensity in the parenchyma Yes to either Right or Left

^b If a MRI was done: NGO3 D8,c,d, and e: Yes on either Right for Left for ventricular size enlarged (c), cystic PVL (d) or porencephalic/posthemorrhagic cyst/multicystic encephalomalacia (e); If a MRI was not done: the same items as above for sonograms after day 28 (NGO3 items 7 c, d, and e).

^c NGO7 A 6 highest FiO_2 on day, column 36 wk: >0.21

^d either NGO3 item F3 proven NEC: 2 or 3 or NGO3 item F4 spontaneous GI perf. Without proven NEC: Yes

^e NGO3 item H1a1 stage 3 or worse in either eye: Yes

We do not propose to assess ABRs as a secondary outcome because: 1) as found in the prior NRN trial, the recording of ABRs and identification of specific waves are difficult to perform reliably in very premature infants, and personnel skilled in assessing them are available in few sites⁵⁶; 2) the ABRs in our dose-finding trial suggest that even transient bilirubin neurotoxicity is unlikely with the cycled PT regimen to be tested; and 3) ABR abnormalities may reflect only transient toxicity; 4) NDI at 2 years will be assessed for infants <27 weeks gestation as part of routine NRN follow-up.

Most of these outcomes are already collected as GDB items. Other outcomes—e.g., TB values, total PT hours (as determined from nursing notes when PT is started and stopped and what regimen is prescribed), irradiance during PT (as recorded on the chart by bedside nurses as part of routine clinical care)—can be assessed by the coordinators from a single chart review at or soon after the infants is discharged.

Post-discharge - NDI, its components, and either Death or NDI (primary follow-up outcome) will be obtained as part of the generic follow-up assessments for infants <27 wks gestation.

4.2.9 Study Specimens. No additional blood sampling will be performed.

4.2.10 Post-Hospital Procedures. Not applicable before follow-up at 24-months.

4.2.11 Follow-Up at 24 Months. Routine generic assessments at 24 months for infants <27 weeks GA.

4.2.12 Additional Follow-Up Assessments. A small proportion of infants ≤ 750 g but ≥ 27 wks GA (10% in our dose-finding study) who are not involved in generic NRN follow-up may be given the same assessments if funding is obtained as part of a secondary study. .

4.3 Potential Risks and Benefits to Subjects. This is a safety study comparing conventional continuous PT to cycled PT, a treatment option since the early 1970s that may be safer in avoiding unnecessary exposure to PT and reducing the risk of death or other short-term or long-term recognized or unrecognized hazards of PT in extremely premature infants. Six prior trials and our multicenter dose-finding study with 305 ELBW infants have shown that cycled PT results in minimal increase in TB above that with conventional PT for ELBW infants. Moreover, our assessment of brainstem auditory evoked responses—a sensitive indicator of even transient bilirubin neurotoxicity—has shown no evidence of bilirubin neurotoxicity with cycled PT. Cycled PT might reduce the risk of any PT-induced hemolysis or life threatening illnesses resulting from uninterrupted exposure to PT, the administration of medications that may displace bilirubin from albumin in treating these illnesses, or other direct or indirect adverse effects of uninterrupted exposure to PT that increase the risk of bilirubin neurotoxicity at a given TB. For reasons specified above, it is entirely possible the cycled PT reduces the risk of bilirubin neurotoxicity at a specific peak TB value.

Thus, there are no foreseeable incremental risks of cycled PT in treating the intervention group. There are also no foreseeable incremental risks of AgPT in treating the control group above the risks of any PT regimen that would be used in the absence of the trial. AgPT is now exclusively used in administering PT to extremely premature infants in 7 NRN centers and is a treatment option in other NRN centers where the PT regimen used is left to the discretion of the attending neonatologist. Our survey of NRN centers suggests that no one is prescribing use of ConPT. PT regimens other than AgPT or ConPT have not been tested in any major clinical trial, and it is unclear whether any regimens that these neonatologists would prescribe have a risk/benefit ratio that is greater, less, or equal to that of AgPT.

SECTION 5. ANALYTICAL PLAN AND STUDY INTERPRETATION.

5.1 Analysis Plan. Intention-to-treat analyses will be used. Generalized linear mixed models will be performed to analyze all outcomes and will include treatment group, mechanical ventilation at enrollment (yes; no), and BW (≤ 650 g; >650 g) as covariates with random effects for center and mother (to account for twins or other multiples being randomized to the same treatment group). Bayesian analyses will be performed in evaluating differences in treatment effects overall and in different patient subgroups and centers. The prior relative risk (RR) is conservatively centered at 0.88 (95% credible intervals = 0.4-1.8; Normal [$\log(0.88)$, $sd=0.37$] in the log RR scale) based on the RR of death with conservative PT relative to aggressive phototherapy among all 501-750 g infants ($n=860$ infants) in the Network PT trial. This estimate is comparable to or slightly higher than in the dose-finding pilot to date (0.84) and substantially higher than with no phototherapy among ELBW infants (0.67) and all LBW infants in (0.76) in the Collaborative Trial. We will also conduct analyses using a prior centered at RR of 1.0 (95% credible interval = 0.50-2.0) for no reduction in mortality despite the results of the prior trials.

For binary outcomes other than death, all priors will be centered at RR of 1.0 (indicative of no difference between treatment groups will be used with a 95% prior interval of 0.5-2.0 (in the log RR scale a Normal distribution with mean of 0 and variance of 0.37^2). A Normal (0, 10^2) prior will be used for the intercept term and Normal (0, 1) for all other variables in the model. For the standard deviation of the center random effect, a half-Normal (0, 1) prior will be used. Similar neutral informative priors (based on previous NRN PT trial where possible) will be used for non-binary outcomes.

Problems with interpretation of frequentist analyses, and in particular p-values, have been widely recognized.^{57,58,59} In a recent study,⁶⁰ survey data show that even authors publishing in top statistical journals “are often confused about the meaning of p-values.”⁶¹ In their statement on p-values, the American Statistical Association recommends that alternative approaches, including Bayesian methods, be considered.⁶² A growing number of statisticians now strongly question the use of p values,⁶⁴ and Szucs and Ioannidis contend that null hypothesis testing should no longer be the default statistical practice of all biomedical research.⁶⁵ In a recent special issue of the American Statistician, Wasserstein, Schirm, and Lazar recommended that the terms statistically significant and non-significant should be abandoned.⁶⁶ However, we recognize that acceptance of other statistical approaches will take time. Hence, we will also conduct frequentist analyses using the same models as for the Bayesian ones. We will report point estimates, 95% confidence intervals, and p values.

5.2 Sample Size, Power and Projected Recruitment Time. Very large trials with high power are often needed to assess new and previously untested therapies to verify their safety and effectiveness. However, with the findings of the prior two large prior trials of continuous PT, the 6 prior trials of cycled PT, and our dose finding trial, the burden of proof should arguably now be on those who would contend that routine use of continuous PT is necessary and desirable.

We propose to enroll 1700 infants (850 infants/group). Assuming a neutral prior probability for death (which is a conservative prior probability given the findings of 0.88 as noted above in the two prior large trial), this sample size provides >0.70 posterior probability (with 80% Bayesian power) that cycled PT increases survival if the true mortality RR is ≤ 0.90 . This would result in a study duration at the limit of what the NRN is likely to consider reasonably feasible.

This sample size also affords 80% power in frequentist analyses to identify a RR of 0.76 (corresponding to a 5.3% absolute increase in survival to discharge from 78% to 83.3%; number needed to treat = 19). Though it indicates a substantial treatment effect, a true mortality RR of 0.76 is entirely possible. It is not much smaller than the RR of 0.84 among ventilator treated infants ≤ 750 g infants in the NRN trial (when PT was provided without interruption to both treatment groups), higher than the RR of 0.67 among all ELBW infants in the Collaborative PT trial (whose risk of death may not have been very different than among extremely premature infants today), and identical to the RR of 0.76 among all LBW infants in the Collaborative PT Trial (who would presumably be at a much lower risk of any life threatening hazards from PT than infants in the proposed trial).

Based on the most recent GDB data available, enrollment would be completed in 3.9 years if 90% of all infants surviving to 12 hours are eligible and 50% of eligible infants are enrolled (967 infants/yr <27 wks GA $\times 0.9 \times 0.5 = 435$ infants enrolled/yr; 1700 infants total/435 infants/yr = 3.9 yrs). [This calculation omits eligible patients >27 weeks but ≤ 750 g, whose numbers were equal to 10% of our patients <27 wks GA in our dose-finding study.] This enrollment rate would be substantially lower than that in the prior more complicated PT trial

(70%) and in our dose-finding study (65%) despite some personnel limitations limiting enrollment and a narrower time window (enrollment by 24 hours rather than 36 hours age). With the hypothesis that cycled PT reduces mortality and with the commitment to obtaining consent in NRN centers, we believe this consent rate—if not a higher rate—should be achievable for this study.

5.3 Interpretation of Findings. A statistically significant increase in survival to discharge and/or 2-year survival or survival without severe NDI at 2 years in a secondary study would clearly warrant a change in clinical practice. However, such findings would not be the only findings that would justify a recommendation to routinely use cycled PT for infants ≤ 750 g BW or <27 weeks GA.

As emphasized above, there is no basis to assume that continuous exposure to bright light is innocuous for translucent, immature, and often quite sick infants, and there is increasing recognition of the known and potential hazards of PT¹⁻¹⁷ including DNA damage and the possibility of an increased risk of cancer in childhood^{16,17,17a} or later life. Given the minimal increase in TB with cycled PT in 6 prior trials and our multi-center dose-finding study (which included the second largest number of ELBW infants studied to date), the reassuring BAER findings we identified, and the high probability of an increased mortality in the only two large trials of continuous PT, the burden of proof is now on those who would recommend routine use of continuous PT for extremely premature infants. Based on the widely accepted maxims to first do no harm and to use the lowest effective dose or exposure to a therapy to minimize the risk of known or unidentified short- or long-term treatment hazards, routine use of cycled PT can be justified for extremely premature infants if the trial finds:

- little difference in peak TB between treatment groups,
- no important increase in major neonatal morbidities with cycled PT, and
- a non-significant increase in survival to discharge with an equal or nonsignificant increase in survival without NDI (identified in follow-up assessments) relative to that with continuous PT.

In this circumstance, the Bayesian posterior probability of $>50\%$ that survival was increased or survival without severe NDI was increased would justify routine use of cycled PT.

5.4 Study Monitoring Plan and Stopping Guidelines. As indicated above, the safety of cycled PT is supported by a) the prior large PT trials indicating a high probability of an increased mortality with greater light exposure b) the minimal difference in TB levels in our dose-finding cycled PT trial and in cycled PT trials in larger infants; c) the BAER findings providing no evidence of bilirubin neurotoxicity with cycled PT in our dose findings study; d) the expectation that the likelihood of adverse effects from a medication or other exposure would be reduced by reducing the dose or exposure. Moreover, any unexpected hazard (e.g., higher NDI) would most likely require assessment of follow-up findings at 2 years. Thus, the numerous interim analyses needed to stop enrollment for neonatal hazards of new therapies never assessed in prior trials would be unwarranted for assessing cycled PT.

Repeated interim analyses would also seem unwarranted for the purpose of stopping enrollment due to the hazards of continuous PT because 1) continuous PT is the conventional therapy in NICUs; 2) the target sample size is limited to that needed to identify a $\geq 70\%$ posterior probability of an increased mortality rather than a statistically significant increase in mortality with continuous PT over cycled PT; 3) the effect size identified in trials stopped early is likely to be larger than the true effect size, and a trial in which enrollment was stopped early might well be too small to convince the neonatology community to rely on the results; 4) stopping the trial early would reduce the probability of identifying any important difference between groups in the percent of survivors who are impaired or profoundly impaired at follow-up.

For all these reasons we propose a single interim Bayesian analysis when half of the patients reach status with enrollment stopped for benefit only for a $> 95\%$ probability of increased survival with cycled PT with a prior centered at 1.0, provided there is no evidence of an increase in death or major morbidity (increased evidence would be a posterior median [under neutral prior] RR >1.20 for death or severe ICH, PVL, BPD, late onset sepsis, NEC or spontaneous intestinal perforation, $>$ stage 3 ROP) in patients randomized to cycled PT. Given the prior evidence of an increased mortality with continuous PT and the play of chance, stopping for an unexpected increase in mortality with cycled PT would be appropriate only if there were strong evidence of such an increase in mortality. The investigators would recommend stopping enrollment early for harm only if there were a $>95\%$ posterior probability of an increased mortality risk with cycled PT using a prior centered at RR of 0.88. Alternatively, a decision to stop enrollment based on mortality findings could be based on a meta-analysis combining the results for mortality from major prior trials comparing more liberal vs. more conservative use of PT.

5.5 Adverse Events. The adverse events are exchange transfusion, death, a clinical diagnosis of acute bilirubin encephalopathy or bilirubin induced neurologic dysfunction. (The latter two adverse are expected to be rare and uncertain diagnoses that cannot be standardized across Network centers.) Study coordinators will be expected only to report these as adverse events when noted by the attending physician. Kernicterus identified at autopsy will also be recorded although its prevalence and importance will be obscured by the infrequency of autopsies and concern that bilirubin staining in the basal ganglia may occur simply as a terminal event.

SECTION 6. TRIAL STRENGTHS AND LIMITATIONS

We propose a simple, important, and relatively inexpensive trial of cycled PT to reduce avoidable deaths in extremely premature infants. Its feasibility has been well demonstrated in our dose-finding study in NRN centers showing that the cycled PT regimen to be tested substantially reduces the duration of PT and results in low peak TB values with no BAER evidence of bilirubin neurotoxicity. The trial would be compatible with other NRN studies and builds on a prior major NRN trial to address the dilemma of offsetting rates of death and of NDI identified by that study. Most importantly, it addresses a major safety issue for a therapy administered to virtually all extremely premature infants.

An unavoidable limitation of the study is that neither caregivers nor parents can be blinded to the PT regimen being used. However, the laboratory personnel who perform TB determinations will be unaware of treatment group. The personnel who assess neurodevelopmental outcomes at 2 years will also be blinded to treatment group. If our hypotheses are all confirmed, we expect that cycled PT would justifiably become the method routinely used in extremely premature infants. The most important limitation to the success of the trial is that as in any clinical trial, the intervention—cycled PT—may not prove to have any important benefit. Bilirubin has antioxidant properties. At least as infants are treated in current neonatal ICUs, any intervention that lowers the TB of extremely premature infants and lowers their risk of NDI in survivors might unavoidably increase their mortality due to oxidative injury. We doubt that this is the case, in part because the risk of BPD was lower—not higher—with AgPT than with ConPT in ELBW infants in the NRN PT trial.

Even if we find little or no evidence of a lower predischARGE mortality or an increase in survival without impairment in a secondary study the trial would still advance the field. Such findings would not obviate the 92% probability that PT increased deaths among ELBW infants in the NICHD Collaborative PT trial in which control infants received no PT. Reducing the total duration of PT by ~50% as we expect in the cycled PT trial may be sufficient to avoid PT-related deaths. Providing no evidence of bilirubin neurotoxicity was identified, a future trial might then evaluate a further reduction in PT exposure (perhaps a regimen of ≥ 10 minutes PT per hour) or the administration of mesoporphyrin compounds to minimize bilirubin formation.¹⁵ This therapy is expected to be ready for testing in clinical trials in high-risk babies no later than when the cycled PT trial would be completed and might increase the survival of small premature infants without NDI by virtually eliminating the use of PT and/or lowering TB values below those with either cycled or continuous PT.

SECTION 7. REFERENCES

- ¹ Stevenson DK, Wong RJ, Arnold CC, Pedroza C, Tyson JE. Phototherapy and the Risk of Photo-Oxidative Injury in Extremely Low Birth Weight (ELBW) Infants. *Clin Perinatol*. 2016 Jun;43(2):291-5
- ² Aycicek A, Erel O. Total oxidant/antioxidant status before and after phototherapy. *J Pediatr (Rio J)*. 2007;83:31922.
- ³ Demirel G, Uras N, Celik IH, et al. Comparison of total oxidant/antioxidant status in unconjugated hyperbilirubinemia of newborns before and after conventional and LED phototherapy: a prospective randomized controlled trial. *Clin Invest Med* 2010; 33:335.
- ⁴ Shekeeb SM, Kumar P, Sharma N. Evaluation of oxidant and antioxidant status in term neonates. *Mol Cell Biochem* 2008;317.
- ⁵ Kurt A, Aygun AD, Kurt ANC, et al. Use of phototherapy for neonatal hyperbilirubinemia affects cytokine production and lymphocyte subsets. *Neonatology*. 2009;95:262.
- ⁶ Faddan N, El-Aziz N, El-Azeem H, Shreif T. Effect of Phototherapy on Blood Levels of Endothelin-1 and Nitric Oxide in Hyperbilirubinemic Newborn Infants. *E-J Neonatol Res*. 2014;4:14.
- ⁷ Benders MJ, et al. The effect of phototherapy on cerebral blood flow velocity in preterm infants. *Acta Paediatr*. 1998;87:786.
- ⁸ Yao AC, Martinussen M, Johansen OJ, Brubakk AM. Phototherapy-associated changes in mesenteric blood flow response to feeding in term neonates. *J Pediatr*. 1994;124:309.
- ⁹ Pezzati M, et al. Changes in mesenteric blood flow response to feeding: conventional vs. fiber-optic PT. *Pediatrics*. 2000;105:350.
- ¹⁰ Baskol G, Saraymen R, et al. Assessment of DNA damage and plasma catalase activity in healthy term hyperbilirubinemic infants receiving phototherapy. *Mutat Res*. 2009;680:12.
- ^{10a} Aycicek A, Kocyigit A, Erel O, Senturk H. Phototherapy causes DNA damage in peripheral mononuclear leukocytes in term infants. *J Pediatr (Rio J)* 2008; 84: 141.
- ^{10b} Ramy N, Ghany EA, Nada A, et al. Jaundice, phototherapy, and DNA damage in full-term neonates. *J Perinatol* 2016; 36: 132.
- ¹¹ Yahia S, Shabaan AE, Gouda M. Influence of hyperbilirubinemia and phototherapy on markers of genotoxicity and apoptosis in full-term infants. *Eur J Pediatr*. 2015;174:459.
- ¹² Karadag A, Yesilyurt A, Unal S, et al. A chromosomal-effect study of intensive phototherapy versus conventional phototherapy in newborns with jaundice. *Mutation Res* 2009;676:17.
- ¹³ Tozzi E et al. In vitro and in vivo effects of erythrocyte phototherapy on newborns. *Biol Neonate*. 1989;56:204.
- ¹⁴ Sisson TR. Photodegradation of riboflavin in neonates. *Fed Proc*. 1987;46:1883.
- ¹⁵ Vreman HJ, Wong RJ, Stevenson DK. Phototherapy: current methods and future directions. *Semin Perinatol* 2004;28(5):326-333.
- ¹⁶ Wickremasinghe AC, Kuzniewicz MW, Grimes BA et al. Neonatal Phototherapy and Infantile Cancer. *Pediatrics*. 2016 Jun;137. pii: e20151353. doi: 10.1542/peds.2015-135.
- ¹⁷ Newman TB, Wickremasinghe AC, Walsh EM, Grimes BA, McCulloch CE, Kuzniewicz MW. Retrospective cohort study of phototherapy and childhood cancer in northern California. *Pediatrics*. 2016 Jun;137.pii: e20151354.
- ^{17a} Tyson JE, Miller CC. Whether neonatal phototherapy increases the risk of cancer in children is a disturbing unresolved issue. *Evid Based Med* 2017;22: 39-40,
- ¹⁸ Oh W, Stevenson DK, Tyson JE et al. Influence of clinical status on the association between plasma total and unbound bilirubin and death or adverse neurodevelopmental outcomes in extremely low birth weight infants. *Acta Paediatr*. 2010 May;99(5):673-8
- ¹⁹ Tyson JE, Pedroza C, et al. Does aggressive phototherapy increase mortality while decreasing profound NDI among the smallest and sickest newborns? *J Perinatol*. 2012;32:677-84
- ²⁰ Morris BH, Oh W, Tyson JE, et al. Aggressive vs. conservative phototherapy for infants with ELBW. *N Engl J Med* 2008;359:1885-96.
- ²¹ Maisels MJ. Chapter 22. Neonatal jaundice. In: Sinclair JC, Bracken MB, eds. *Effective care of the newborn infant*. Oxford, England: Oxford University Press, 1992: Table 47, p 532.
- ²² Arnold C, Pedroza C, Tyson J. Phototherapy in ELBW infants: Does it work? Is it safe? The evidence from RCTs. *Semin Perinatol*. 2014;38:452.
- ²³ Maisels MJ¹, Watchko JF, Bhutani VK, Stevenson DK An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. *J Perinatol*. 2012;32:660-4.

- 24 Scheidt PC, Graubard BI, Nelson KB, et al. Intelligence at six years in relation to neonatal bilirubin level. Follow-up of the NICHD clinical trial of phototherapy. *Pediatrics* 1991;87:797-805.
- 25 Poland RL. Phototherapy for neonatal hyperbilirubinemia. *Pediatrics* 1986;78:179-180
- 26 Bryla DA, Brown A, Gartner L, Lipsitz P. In reply. *Pediatrics* 1986;180-181
- 27 Silverman WA. Human experimentation in perinatology. *Clin Perinatol* 1987;14:403-16.
- 28 Prasad V, Cifu A, Ioannidis JP. Reversals of established medical practices: evidence to abandon ship. *JAMA* 2012; 307: 37-9.
- 29 Shankaran S, Laptook AR, Pappas A, et al. Effect of Duration of Cooling on Deaths in the NICU among neonates with hypoxic ischemic encephalopathy. A randomized clinical trial. *JAMA* 2014; 312:2629-39.
- 30 Ioannidis JP. Why most discovered true associations are inflated. *Epidemiology* 2008;19:640-648
- 31 Ioannidis JP. Contradicted and initially stronger effects in highly cited clinical research. *JAMA* 2005;294:218-228.
- 31a Lamola AA. A pharmacologic view of phototherapy. *Clin Perinatol* 2016; 43:259.
- 32 Lucey JF. Neonatal jaundice and phototherapy. *Pediatr Clin N Amer* 1972;19 (4): 827
- 33 Cremer RJ, Perryman PW, Richards DH. Influence of light on the hyperbilirubinemia of infants. *Lancet* I:1094, 1958.
- 34 Zachman D. Alternate phototherapy in neonatal hyperbilirubinemia. *J Pediatr* 1972; 178.
- 35 Vogl TP, Hegyi T, Hiatt IM, et al. Intermediate phototherapy in the treatment of jaundice in the premature infant. *J Pediatr*. 1978; 92:627.
- 36 Lau SP, Fung KP. Serum bilirubin kinetics in intermittent phototherapy. *Arch Dis Child*. 1984;59:892.
- 37 Niknafs P et al. Intermittent versus continuous phototherapy for reducing neonatal hyperbilirubinemia. *Iran J Pediatr*. 2008;18:251.
- 38 Sachdeva M, Srinivas M, Oleti TP, Kandragu H. Intermittent versus continuous phototherapy for the treatment of neonatal non-hemolytic moderate hyperbilirubinemia in infants more than 34 weeks of gestational age: a randomized controlled trial. *Eur J Pediatr* 2015;174:177.
- 39 Santella RM, Rosenkranz HS, Speck WT. Intracellular deoxyribonucleic acid-modifying activity of intermittent phototherapy. *J Pediatr* 1978; 93:106-9.
- 40 Tatli MM¹, Minnet C, Kocyigit A, Karadag A. Phototherapy increases DNA damage in lymphocytes of hyperbilirubinemic neonates. *Mutat Res*. 2008 Jun 30;654(1):93-5. doi: 10.1016/j.mrgentox.2007.06.013. Epub 2008 Apr 18.
- 41 Kahveci H, Dogan H, Karaman A, et al. Phototherapy causes transient DNA damage in jaundiced newborns. *Drug Chem Toxicol*. 2013 Jan;36(1):88-92.
- 42 Morris BH, Tyson JE, Stevenson DK, et al. Efficacy of phototherapy devices and outcomes among extremely low birth weight infants: a multi-center observational study. *J Perinatol* 2012; 1.
- 43 Shapiro SM, Popelka GR. Auditory impairment in infants at risk for bilirubin-induced neurologic dysfunction. *Semin Perinatol* 2011; 35:162-70.
- 44 Deorari AK, Singh M, Ahuja GK et al. One year outcome of babies with severe neonatal hyperbilirubinemia and reversible abnormality in brainstem auditory evoked responses. *Indian Pediatr* 1994;31:915.
- 45 Wennberg RW, Ahlfors CA, Bickers R, et al. Abnormal auditory brainstem response in a newborn infant with hyperbilirubinemia: Improvement with exchange transfusion. *J Pediatr* 1982;100:624.
- 46 Kuriyama M, Tomwas K, Konishi Y, Mikawa H. Improvement in auditory brainstem response of hyperbilirubinemic infants after exchange transfusion. *Pediatr Neurol* 1986;2:127.
- 46a Rice-Evans, C.A., Measurement of total antioxidant activity as a marker of antioxidant status *in vivo*: procedures and limitations. *Free Radic. Res.*, **33** Suppl, S59-66 (2000).
- 46b Proteggente, A.R., et al., Gender differences in steady-state levels of oxidative damage to DNA in healthy individuals. *Free Radic. Res.*, **36**, 157-162 (2002).
- 46c Huang, H., et al., The chemistry behind antioxidant capacity assays. *J. Agric. Food Chem.*, **53**, 1841- 1856 (2005).
- 46d Saenz-de-Viteri M, Heras-Mulero H, Fernández-Robredo P, Recalde S, Hernández M, Reiter N, Moreno-Orduña M, García-Layana A. Oxidative stress and histological changes in a model of retinal phototoxicity in rabbits. *Oxid Med Cell Longev*. 2014;2014:63713
- 46e Mannan J, Amin SB Meta-Analysis of the effect of chest shielding on preventing patent ductus arteriosus in premature Infants. *Am J Perinatol* 2017; 34:359-63.
- 47 Rivkees SE, Hao H. Developing circadian rhythmicity. *Semin Perinatol* 2000;21:232.
- 48 Penn AA, Shatz CJ. Brain waves and brain wiring: The role of endogenous and sensory-driven neural activity in development. *Pediatr Reserqch* 1999;45L447-58
- 49 Hao H, Rivkees SA. The biological clock of very premature infants is responsive to light. *Proceed Nat Acad Sci* 1999;96:2426.
- 50 Seron-Ferre M, Torres C, Parraguez VH et al. Perinatal neuroendocrine regulation. Development of the circadian time keeping system. *Molecular Cellular Endocrin* 2002;21L232.

-
- ⁵¹ Kramer MS, Mclean FH, Boyd ME, Usher RH. The validity of gestational age estimation by menstrual dating in preterm, term, and postterm gestations. *JAMA* 1988;260:3306-8.
- ⁵² Gjessing HK, Skjoerven R, Wilcox AJ. Errors in gestational age: evidence of bleeding early in pregnancy. *Am J Public Health* 1999;89:213-8
- ⁵³ Wilcox AJ, Dunson D, Baird DD. The timing of the “fertile window” in the menstrual cycle: day specific estimates from a prospective study. *BMJ* 2000;321:1259-62
- ⁵⁴ Kramer MS, Platt RW, Wen SW, et al. A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics* 2001;108:E35
- ⁵⁵ Tyson JE, Parikh NA, Langer J, Green C, Higgins RD, National Institute of Child Health and Human Development Neonatal Research Network. Intensive care for extreme prematurity--moving beyond gestational age. *N Engl J Med*. 2008 Apr 17;358(16):1672-81.
- ^{55a} Odell GB, Brown RS, Kopelman AE. The photodynamic action of bilirubin on erythrocytes. *J Pediatr* 1972;81:473.
- ^{55b} Chandler BD, Cashore WJ, Monin PJP, Oh W. The lack of effects of phototherapy on neonatal oxygen dissociation curves and hemoglobin concentration in vivo. *Pediatrics* 1977; 59:1027-31.
- ⁵⁶ Lasky RE, Church MW, Orlando MS, et al. The effects of aggressive vs. conservative phototherapy on the brainstem auditory evoked responses of extremely-low-birth-weight infants. *Pediatr Res*. 2012; 71:77-4.
- ⁵⁷ McShane, B.B. and Gal, D., 2015. Blinding us to the obvious? The effect of statistical training on the evaluation of evidence. *Management Science*, 62(6), pp.1707-1718.
- ⁵⁸ Gelman A, Loken E. The statistical crisis in science. *Am. Sci.* 2014;102:460.
- ⁵⁹ Nuzzo R. Scientific method: Statistical errors. *Nature*. 2014;506:150–2.
- ⁶⁰ McShane, B.B. and Gal, D., Statistical significance and the dichotomization of evidence. To appear. *Journal of the American Statistical Association*
- ⁶¹ Gelman A and Carlin J. Some natural solutions to the p-value communication problem— and why they won’t work. In Discussion of “Statistical significance and the dichotomization of evidence,” *J Amer Stat Assoc*.
- ⁶² Wasserstein RL, Lazar NA. The ASA’s statement on p-values: context, process, and purpose. *Amer Stat* 2016;70:129–33.
- ⁶⁴ Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature*. 2019;567:305-307.
- ⁶⁵ Szucs D, Ioannidis JPA. When Null Hypothesis Significance Testing Is Unsuitable for Research: A Reassessment. *Front Hum Neurosci*. 2017 Aug 3;11:390.
- ⁶⁶ Wasserstein RL, Schirm AL, Lazar NA. Moving to a world beyond “ $p < 0.05$.” *Amer Stat* 2019; 73 S:11-19.