Appendix of Supplemental Materials

Supplemental Figure S1:
Flow diagram of patient enrollment

Supplemental Figure S2:
Mean hemoglobin values available for the 124 enrolled subjects with NIRS data in the first week of life and 95% confidence intervals. Percent of all subjects with measured hemoglobin at each day of life are included above each datapoint.

Supplemental Table S1:
Estimates of mean NIRS measures during the first week of life by week of gestational age.

Supplemental Table S2:
Perinatal variables differentially affect cerebral and mesenteric NIRS estimates at 96 hours.

Supplemental Figure S3:
Predicted NIRS measures in the first week stratified by hemoglobin transfusion threshold group are shown using cubic regression lines with 95% confidence intervals.

Supplemental Table S3:
Additional investigators from participating sites of the NICHD Neonatal Research Network
Supplemental Figure 1: Flow Diagram of Enrollment

Eligible for enrollment, n=409

- Not consented (17)
- Refused consent (143)

Consented to NIRS Monitoring Ancillary Study, n=249

- Equipment unavailable or not functioning (6)
- Staff unavailable (1)
- Infant inaccessible, died, or too ill to apply NIRS sensor (16)
- Not monitored in 1st week due to skin fragility or other reason (47)

Enrolled in NIRS Monitoring Ancillary Study, n=179

NIRS data not acquired or lost (15)

NIRS monitoring data available, n=164

- Data invalid (1)
- Data only available beyond first week of life (39)

Valid NIRS data available for 1st week of life, n = 124
Supplemental Figure 2:
All Measured Hemoglobin Values through the First Week of Life (N=124)
### Supplemental Table 1: Estimates of First Week Mean NIRS Measures by Gestational Age

| Gestational Age (weeks) | Csat (%), n=124 | cFTOE, n=113 | Msat (%), n=97 | mFTOE, n=85 |
|-------------------------|----------------|--------------|----------------|-------------|
|                         | Estimate | Lower 95% C.L. | Upper 95% C.L. | Estimate | Lower 95% C.L. | Upper 95% C.L. | Estimate | Lower 95% C.L. | Upper 95% C.L. |
| 23                      | 49.0     | 37.5          | 60.5           | 0.46     | 0.35          | 0.58           | 61.7     | 44.7          | 78.7           |
| 24                      | 58.6     | 51.4          | 65.7           | 0.33     | 0.25          | 0.41           | 47.9     | 32.5          | 63.4           |
| 25                      | 65.8     | 60.4          | 71.3           | 0.28     | 0.22          | 0.34           | 48.3     | 40.9          | 55.7           |
| 26                      | 64.6     | 59.7          | 69.5           | 0.32     | 0.26          | 0.37           | 43.3     | 36.9          | 49.7           |
| 27                      | 66.5     | 60.9          | 72.2           | 0.29     | 0.23          | 0.35           | 43.3     | 36.2          | 50.5           |
| 28                      | 69.2     | 62.4          | 76.1           | 0.27     | 0.20          | 0.34           | 39.2     | 30.3          | 48.1           |

*All estimates are adjusted for the random effect of infant.*
Supplemental Table 2 – NIRS Estimates at 96 hours (N=124)\(^a\)

| Variable                                | Csat Mean (95% CI) | Csat Ref Mean\(^b\) (95% CI) | p-value\(^c\) | cFTOE Mean (95% CI) | cFTOE Ref Mean\(^b\) (95% CI) | p-value\(^c\) | Msat Mean (95% CI) | Msat Ref Mean\(^b\) (95% CI) | p-value\(^c\) | mFTOE Mean (95% CI) | mFTOE Ref Mean\(^b\) (95% CI) | p-value\(^c\) |
|-----------------------------------------|--------------------|-------------------------------|--------------|---------------------|-------------------------------|--------------|--------------------|-------------------------------|--------------|---------------------|-------------------------------|--------------|
| Low Hb Threshold                        | 62.9 (59.2, 66.7)  | 66.0 (62.3, 69.8)             | .0001        | 0.32 (0.28, 0.36)   | 0.29 (0.25, 0.33)             | .0001        | 42.3 (37.2, 47.5) | 47.0 (41.9, 52.0)              | .0001        | 57.6 (51.5, 63.8) | 51.8 (45.9, 57.7)              | .0001        |
| 2+ Transfusions                         | 60.6 (55.8, 65.5)  | 66.1 (63.0, 69.2)             | .0001        | 0.34 (0.29, 0.39)   | 0.29 (0.26, 0.32)             | .0001        | 50.0 (42.8, 56.3) | 42.8 (38.6, 47.0)              | .0001        | 0.48 (0.40, 0.57) | 0.57 (0.52, 0.62)              | .0001        |
| Low Hb threshold/ 2+ transfusions       | 54.0 (46.2, 61.9)  | 65.8 (63.0, 68.5)             | .0001        | 0.42 (0.33, 0.51)   | 0.29 (0.26, 0.32)             | .0001        | 45.6 (32.3, 59.0) | 44.6 (40.9, 48.4)              | .0001        | 0.55 (0.38, 0.73) | 0.54 (0.50, 0.59)              | 0.02         |
| Male Sex                                | 64.8 (60.6, 69.0)  | 64.3 (60.9, 67.7)             | .22          | 0.29 (0.25, 0.34)   | 0.31 (0.27, 0.35)             | 0.83         | 43.4 (37.6, 49.2) | 45.4 (40.8, 50.0)              | 0.03         | 0.58 (0.51, 0.65) | 0.53 (0.47, 0.58)              | 0.83         |
| SGA                                     | 64.1 (56.2, 72.0)  | 64.6 (61.7, 67.4)             | .0001        | 0.34 (0.25, 0.42)   | 0.30 (0.27, 0.33)             | 0.0005       | 40.9 (30.3, 51.6) | 45.2 (41.3, 49.0)              | 0.001        | 0.59 (0.47, 0.72) | 0.54 (0.49, 0.59)              | 0.10         |
| Lower GA                                | 61.4 (57.2, 65.5)  | 66.5 (63.2, 69.9)             | .001         | 0.32 (0.28, 0.37)   | 0.29 (0.26, 0.33)             | .0001        | 49.6 (43.3, 56.0) | 42.4 (38.1, 46.7)              | 0.09         | 0.50 (0.43, 0.58) | 0.56 (0.51, 0.61)              | .0001        |
| Lower BW                                | 62.2 (58.5, 66.0)  | 66.6 (62.9, 70.3)             | 0.0017       | 0.32 (0.28, 0.36)   | 0.29 (0.25, 0.33)             | 0.98         | 47.0 (41.5, 52.4) | 42.9 (38.1, 47.7)              | 0.03         | 0.53 (0.46, 0.59) | 0.56 (0.50, 0.62)              | 0.003        |
| 5-min Apgar ≤5                          | 61.5 (55.2, 67.9)  | 64.9 (62.0, 67.9)             | 0.23         | 0.35 (0.28, 0.42)   | 0.30 (0.27, 0.33)             | 0.28         | 48.3 (39.8, 56.8) | 43.5 (39.5, 47.5)              | .0001        | 0.49 (0.39, 0.59) | 0.56 (0.51, 0.61)              | 0.001        |

\(^a\) All 96-hour estimates are adjusted for the random effect of subject within center, with gestational age and birth weight as continuous variables; \(^b\) Ref mean is comparison group reference mean; \(^c\) p-value is for test of interaction of each variable with time across the entire first week.

- Green = Csat and Msat both lower than reference group (cerebral and mesenteric measures trend together)
- Yellow = Csat lower than reference group, but Msat higher than reference group (cerebral and mesenteric measures have opposite trends)
- White = No significant difference in cerebral and mesenteric measures between group
Supplemental Figure 3: NIRS Changes by Hemoglobin Transfusion Threshold Group

- **Csat (%)**
  - X-axis: Day of Life
  - Y-axis: Csat (%)
  - Two lines represent different threshold groups:
    - High Hgb Threshold
    - Low Hgb Threshold

- **Msat (%)**
  - X-axis: Day of Life
  - Y-axis: Msat (%)
  - Two lines represent different threshold groups:
    - High Hgb Threshold
    - Low Hgb Threshold

- **cFTOE**
  - X-axis: Day of Life
  - Y-axis: cFTOE
  - Two lines represent different threshold groups:
    - High Hgb Threshold
    - Low Hgb Threshold

- **mFTOE**
  - X-axis: Day of Life
  - Y-axis: mFTOE
  - Two lines represent different threshold groups:
    - High Hgb Threshold
    - Low Hgb Threshold
Supplemental Table 3: Additional Investigators of the NICHD Neonatal Research Network

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| --- |
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