## **Supplemental Online Content**

Zhu X, Li F, Shi Y, Feng Z, De Luca D; Nasal Oscillation Post-Extubation (NASONE) Study Group. Effectiveness of nasal continuous positive airway pressure vs nasal intermittent positive pressure ventilation vs noninvasive high-frequency oscillatory ventilation as support after extubation of neonates born extremely preterm or with more severe respiratory failure: a secondary analysis of a randomized clinical trial. *JAMA Netw Open.* 2023;6(7):e2321644. doi:10.1001/jamanetworkopen.2023.21644

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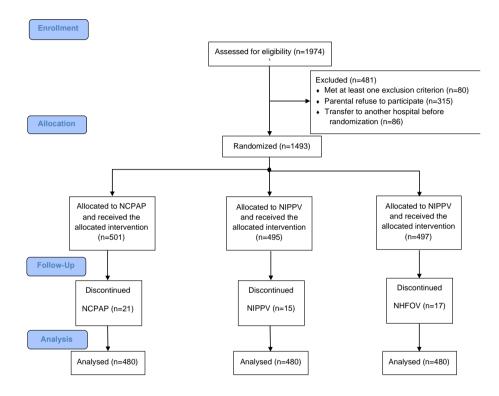
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This supplemental material has been provided by the authors to give readers additional information about their work.

**eFigure 1. CONSORT Flowchart of the Original NASONE Trial.** For the 80 neonates who met an exclusion criterion, the distribution was as follows: grade-IV IVH (n=21), major congenital anomalies/chromosomal abnormalities (n=9), upper respiratory tract abnormalities (n=11), need for surgery known before the first extubation (n=35), birth weight <600g (n=4). The allocated treatment was discontinued in 53 neonates because their parents/guardians withdrew their consent to participation in the trial.



eTable 1. Basic Characteristics of Population Subgroups Complementary to the Subgroups of Interest (i.e.: Subgroups With More Mature Neonates and Those With Less Severe Respiratory Failure). Data are expressed as mean (standard deviation) or number (%). Prenatal steroid is considered if complete (two 12 mg doses of betamethasone, 24 h apart from each other). Surfactant replacement was always performed by intubation-surfactant-extubation technique. CRIB-II, OI and pH are dimensionless variables. Abbreviations: CRIB-II: Clinical Risk Index for Babies-II score; FiO<sub>2</sub>: inspired oxygen faction; NCPAP: nasal continuous positive airway pressure; NHFOV: noninvasive high-frequency oscillation ventilation; NIPPV: noninvasive positive pressure ventilation; OI: oxygenation index (OI=(FiO<sub>2</sub>×Paw)×100/PaO<sub>2</sub>); PaCO<sub>2</sub>: partial pressure of carbon dioxide; PaO<sub>2</sub>: partial oxygen pressure; Paw: mean airway pressure; SGA: small for gestational age.

|                         | >28 weeks' gestation |                  |                  |      | Ventilated       | < 1week fro      | om birth         |      | CO <sub>2</sub> ≤ 50mmHg before or in the 24h after the extubation |                  |                  |      |  |
|-------------------------|----------------------|------------------|------------------|------|------------------|------------------|------------------|------|--|------------------|------------------|------|--|
|                         | NCPAP<br>(N=346)     | NIPPV<br>(N=320) | NHFOV<br>(N=319) | p    | NCPAP<br>(N=370) | NIPPV<br>(N=349) | NHFOV<br>(N=346) | p    | NCPAP<br>(N=357)   | NIPPV<br>(N=386) | NHFOV<br>(N=390) | p    |  |
| Gestational age (weeks) | 30.4<br>(1.1)        | 30.4<br>(1.1)    | 30.5<br>(1.1)    | 0.55 | 29.7<br>(1.6)    | 29.5<br>(1.8)    | 29.6<br>(1.8)    | 0.22 | 29.7<br>(1.6)  | 29.4<br>(1.8)    | 29.5<br>(1.8)    | 0.17 |  |
| Birth<br>weight (g)     | 1441<br>(298)        | 1482<br>(343)    | 1461<br>(330)    | 0.27 | 1382<br>(304)    | 1358<br>(353)    | 1369<br>(362)    | 0.64 | 1378<br>(318)  | 1340<br>(359)    | 1348<br>(353)    | 0.29 |  |
| Male<br>sex             | 191<br>(55.2%)       | 192<br>(60%)     | 198<br>(62%)     | 0.18 | 214<br>(57.8%)   | 213<br>(61%)     | 215<br>(62.1%)   | 0.47 | 203<br>(56.9%)   | 233<br>(60.4%)   | 241<br>(61.8%)   | 0.37 |  |
| SGA<br>neonates         | 36<br>(10.1%)        | 29<br>(9%)       | 21<br>(6.6%)     | 0.21 | 35<br>(9.5%)     | 34<br>(9.7%)     | 22<br>(6.4%)     | 0.21 | 34<br>(9.5%)   | 36<br>(9.3%)     | 26<br>(6.7%)     | 0.28 |  |
| Twins                   | 94 (27.2%)           | 97 (30.3%)       | 97 (30.4%)       | 0.57 | 98<br>(26.5%)    | 110<br>(31.5%)   | 103 (29.8%)      | 0.32 | 102<br>(28.6%)   | 126<br>(32.6%)   | 127<br>(32.6%)   | 0.40 |  |
| Cesarean section        | 210<br>(60.7%)       | 198<br>(61.9%)   | 204<br>(63.9%)   | 0.68 | 202 (54.6%)      | 184<br>(52.7%)   | 180<br>(52%)     | 0.77 | 191<br>(53.5%)   | 211<br>(54.7%)   | 208<br>(53.3%)   | 0.92 |  |
| Prenatal steroids       | 144 (41.6%)          | 161<br>(50.3%)   | 137 (42.9%)      | 0.06 | 161<br>(43.5%)   | 181<br>(51.9%)   | 169<br>(48.8%)   | 0.07 | 149<br>(41.7%)   | 194<br>(50.2%)   | 179<br>(45.9%)   | 0.06 |  |
| CRIB-II<br>score        | 4.1 (2.2)            | 3.9<br>(2.4)     | 4 (2.4)          | 0.58 | 4.7<br>(2.8)     | 4.9<br>(3)       | 5<br>(3.2)       | 0.34 | 4.9<br>(2.9)   | 5.1<br>(3.2)     | 5.3<br>(3.2)     | 0.24 |  |
| 5' Apgar<br>score       | 9<br>[9-10]          | 9<br>[8-10]      | 9<br>[9-10]      | 0.87 | 9<br>[8-10]      | 9<br>[8-10]      | 9<br>[9-10]      | 0.78 | 9<br>[9-10]  | 9<br>[9-10]      | 9<br>[8-10]      | 0.67 |  |
| Surfactant replacement  | 287<br>(82.9%)       | 266<br>(83.1%)   | 259<br>(81.2%)   | 0.77 | 307<br>(83%)     | 296<br>(84.8%)   | 283<br>(81.2%)   | 0.56 | 299<br>(83.8%)   | 330<br>(85.5%)   | 322<br>(82.6%)   | 0.53 |  |
| Early onset sepsis      | 10 (2.9%)            | 6 (1.9%)         | 8<br>(2.5%)      | 0.69 | 8 (2.2%)         | 8 (2.3%)         | 9 (2.6%)         | 0.92 | 7 (2%)   | 7<br>(1.8%)      | 7<br>(1.8%)      | 0.98 |  |

### eAppendix. P Values for Figures

For Figure 1A in the text, for neonates of gestational age 28 or fewer weeks, P = .007 for noninvasive positive pressure ventilation (NIPPV) vs nasal continuous positive airway pressure (NCPAP), and P < .001 for noninvasive high-frequency oscillation ventilation (NHFOV) vs NCPAP. For neonates invasively ventilated for at least 1 week, P < .001 for NIPPV vs NCPAP and NHFOV vs NCPAP. For neonates with CO<sub>2</sub> greater than 50 mm Hg before or in the 24 hours after extubation, P = .003 for NIPPV vs NCPAP, and P < .001 for NHFOV vs NCPAP. For neonates invasively ventilated for at least 1 week, P < .001 for NIPPV vs NCPAP and NHFOV vs NCPAP. For neonates invasively ventilated for at least 1 week, P < .001 for NIPPV vs NCPAP and NHFOV vs NCPAP. For neonates with CO<sub>2</sub> greater than 50 mm Hg before or in the 24 hours after extubation, P < .001 for NIPPV vs NCPAP, and P = .01 for NHFOV vs NCPAP.

For Figure 2A in the text, for the mean difference in IMV duration in neonates of gestational age up to 28 weeks, P = .03 for noninvasive positive pressure ventilation (NIPPV) vs nasal continuous positive airway pressure (NCPAP), and P = .008 for noninvasive high-frequency oscillation ventilation (NHFOV) vs NCPAP. For the mean difference in IMV duration in neonates invasively ventilated for at least 1 week, P < .001 for NIPPV vs NCPAP and NHFOV vs NCPAP, and P = .03 for NIPPV vs NHFOV. For the mean difference in IMV duration in neonates with CO<sub>2</sub> greater than 50 mm Hg before or in the 24 hours after extubation, P = .04 for NHFOV vs NCPAP. For Figure 2B in the text, for the mean difference in ventilator-free days for neonates with CO<sub>2</sub> greater than 50 mm Hg before or in the 24 hours after extubation, P = .04 for NIPPV vs NCPAP.

For Figure 3A in the text, for the difference in risk of BPD in neonates of gestational age 28 or fewer weeks, P = .01 for noninvasive high-frequency oscillation ventilation (NHFOV) vs nasal continuous positive airway pressure (NCPAP). For Figure 3B in the text, for the difference in risk of moderate-to-severe BPD in neonates of gestational age 28 or fewer weeks, P = .04 for NHFOV vs NCPAP. For the difference in risk of moderate-to-severe BPD in neonates invasively ventilated for at least 1 week, P = .02 for NHFOV vs NCPAP. For the difference in risk of moderate-to-severe BPD in neonates with CO<sub>2</sub> greater than 50 mm Hg before or in the 24 hours after extubation, P = .03 for NHFOV vs NCPAP.

For Figure 4A in the text, for the difference in oxygenation index for neonates of gestational age 28 or fewer weeks, P = .001 for noninvasive high-frequency oscillation ventilation (NHFOV) vs nasal continuous positive airway pressure (NCPAP), and P = .05 for noninvasive positive pressure ventilation (NIPPV) vs NHFOV. For the difference in oxygenation index for neonates invasively ventilated for at least 1 week, P = .04 for NHFOV vs NCPAP, and P = .007 for NIPPV vs NHFOV. For the difference in oxygenation index for neonates with CO<sub>2</sub> greater than 50 mm Hg before or in the 24 hours after extubation, P = .005 for NHFOV vs NCPAP, and P = .04 for NIPPV vs NHFOV. For Figure 4B in the text, for the difference in CO<sub>2</sub> for neonates of gestational age 28 or fewer weeks, P = .02 for NHFOV vs NCPAP. For the difference in CO<sub>2</sub> for neonates invasively ventilated for at least 1 week, P = .04 for NIPPV vs NCPAP, and P = .02 for NHFOV vs NCPAP.

**eTable 2. Reasons for Reintubation in the Subgroups.** Raw data are expressed as number (%); differences between study arms are expressed as risk difference (95% CI) for the reintubations. The frequency of refractory hypoxemia in the subgroup of interest is significantly different (neonates  $\le 28^{+6}$  weeks' gestation: overall p=0.006; neonates ventilated  $\ge 1$  week from birth: overall p=0.0003; neonates with CO<sub>2</sub> > 50mmHg before or in the 24h after the extubation: overall p=0.001). **Abbreviations:** NCPAP: nasal continuous positive airway pressure; NHFOV: non-invasive high-frequency oscillation ventilation; NIPPV: noninvasive positive pressure ventilation.

|                             | NCPAP     | NIPPV     | NHFOV     | NCPAP - NIPP\  | <u></u>       | NCPAP - NHFO   | V          | NIPPV - NHFO   | v          |  |
|-----------------------------|-----------|-----------|-----------|----------------|---------------|----------------|------------|----------------|------------|--|
|                             | (N=134)   | (N=160)   | (N=161)   |                | 1 =           | D.166          | T =        | D144           |            |  |
|                             | =(= 00()  | 1(0.50()  | 0(4.00()  | Difference     | Post-hoc p    | Difference     | Post-hoc p | Difference     | Post-hoc p |  |
| Severe respiratory acidosis | 7(5.2%)   | 4(2.5%)   | 3(1.8%)   | 2.7(-1.8;8.1)  | 0.24          | 3.3(-1.0;8.7)  | 0.19       | 0.6(-3.1;4.6)  | 0.72       |  |
| Refractory hypoxemia        | 36(26.9%) | 28(17.5%) | 22(13.7%) | 9.4(-0.1;18.9) | 0.05          | 13.2(4.0;22.4) | 0.005      | 3.8(-4.2;11.8) | 0.34       |  |
| Severe apneas               | 11(8.2%)  | 9(5.6%)   | 7(4.3%)   | 2.6(-3.3;9.0)  | 0.38          | 3.8(-1.8;10.2) | 0.17       | 1.3(-3.8;6.5)  | 0.60       |  |
| Pulmonary hemorrhage        | 1(0.7%)   | 0         | 0         | 0              |               | 0              |            | 0              |            |  |
| Hemodynamic instability     | 1(0.7%)   | 3(1.9)    | 3(1.8%)   | -1.1(-2.4;4.7) | 0.63          | -1.1(-2.5;4.6) | 0.63       | 0(-2.8;2.9)    | >0.99      |  |
| Cardio-respiratory arrest   | 1(0.7%)   | 0         | 0         | 0              |               | 0              |            | 0              |            |  |
| Neonates >28 weeks' gesta   | ation     |           |           |                |               |                |            |                |            |  |
|                             | NCPAP     | NIPPV     | NHFOV     | NCPAP - NIPP\  | 1             | NCPAP - HFOV   |            | NIPPV - NHFOV  |            |  |
|                             | (N=346)   | (N=320)   | (N=319)   | Difference     | Post-hoc p    | Difference     | Post-hoc p | Difference     | Post-hoc p |  |
| Severe respiratory acidosis | 14(4%)    | 4(1.2%)   | 3(0.9%)   | 2.8(0.3;5.5)   | 0.03          | 3.1(0.7;5.8)   | 0.01       | 0.3(-1.6;2.3)  | >0.99      |  |
| Refractory hypoxemia        | 41(11.8%) | 25(7.8%)  | 16(5%)    | 4.0(-0.5;8.6)  | 0.08          | 6.8(2.6;11.1)  | 0.002      | 2.8(-1.1;6.7)  | 0.15       |  |
| Severe apneas               | 5(1.4%)   | 3(0.9%)   | 2(0.6%)   | 0.5(-1.4;2.5)  | 0.73          | 0.8(-1.0;2.7)  | 0.45       | 0.3(-1.4;2.1)  | >0.99      |  |
| Pulmonary hemorrhage        | 1(0.3%)   | 1(0.3%)   | 1(0.3%)   | 0(-1.3;1.5)    | >0.99         | 0(-1.3;1.5)    | >0.99      | 0(-1.3;1.5)    | >0.99      |  |
| Hemodynamic instability     | 4(1.1%)   | 4(1.2%)   | 4(1.2%)   | -0.1(-1.8;2.1) | >0.99         | -0.1(-1.8;2.1) | >0.99      | 0(-2.0;2.0)    | >0.99      |  |
| Cardio-respiratory arrest   | 1(0.3%)   | 3(0.9%)   | 2(0.6%)   | -0.6(-0.8;2.4) | 0.35          | -0.3(-1.4;2.1) | 0.61       | 0.3(-1.4;2.1)  | >0.99      |  |
| Neonates ventilated ≥ 1we   |           |           |           |                |               |                |            |                |            |  |
|                             | NCPAP     | NIPPV     | NHFOV     | NCPAP - NIPP   |               | NCPAP - HFOV   |            | NIPPV - NHFO   |            |  |
|                             | (N=110)   | (N=131)   | (N=134)   | Difference     | Post-hoc p    | Difference     | Post-hoc p | Difference     | Post-hoc p |  |
| Severe respiratory acidosis |           | 2(1.5%)   | 1(0.7%)   | 3.0(-1.6;8.8)  | 0.25          | 3.8(-0.4;9.5)  | 0.09       | 0.8(-2.7;4.7)  | 0.62       |  |
| Refractory hypoxemia        | 31(28.2%) | 16(12.2%) | 14(10.4%) | 16.0(5.8;26.1) | 0.002         | 17.7(7.9;27.6) | <0.001     | 1.8(-6.0;9.6)  | 0.65       |  |
| Severe apneas               | 8(7.3%)   | 6(4.6%)   | 3(2.2%)   | 2.7(-3.5;9.6)  | 0.37          | 5.0(-0.4;11.6) | 0.07       | 2.3(-2.5;7.6)  | 0.33       |  |
| Pulmonary hemorrhage        | 1(0.9%)   | 0         | 0         | 0              |               | 0              |            | 0              |            |  |
| Hemodynamic instability     | 1(0.9%)   | 1(0.7%)   | 0         | >0.99          | 0.1(-3.4;4.2) | 0              |            | 0              |            |  |
| Cardio-respiratory arrest   | 0         | 0         | 0         | 0              |               | 0              |            | 0              |            |  |
| Ventilated < 1week from bi  |           |           |           |                |               | 1              |            |                |            |  |
|                             | NCPAP     | NIPPV     | NHFOV     | NCPAP - NIPP   |               | NCPAP - NHFC   |            | NIPPV - NHFO   |            |  |
|                             | (N=370)   | (N=349)   | (N=346)   | Difference     | Post-hoc p    | Difference     | Post-hoc p | Difference     | Post-hoc p |  |
| Severe respiratory acidosis | 16(4.3%)  | 6(1.7%)   | 5(1.4%)   | 2.6(0.0;5.3)   | 0.04          | 2.9(0.4;5.6)   | 0.02       | 0.3(-1.8;2.4)  | 0.99       |  |
| Refractory hypoxemia        | 46(12.4%  | 37(10.6%) | 24(6.9%)  | 1.8(-2.3;6.5)  | 0.53          | 5.5(1.1;9.8)   | 0.01       | 3.7(-0.6;7.9)  | 0.07       |  |

|                                      |               |                   |                   | ,              |            |                |            |                 |            |  |
|--------------------------------------|---------------|-------------------|-------------------|----------------|------------|----------------|------------|-----------------|------------|--|
| Severe apneas                        | 8(2.1%)       | 6(1.7%)           | 6(1.7%)           | 0.4(-1.8;2.7)  | 0.67       | 0.4(-1.8;2.7)  | 0.68       | 0(-2.2;2.2)     | >0.99      |  |
| Pulmonary hemorrhage                 | 1(0.3%)       | 1(0.3%)           | 1(0.3%)           | 0(-1.3;1.3)    | >0.99      | 0(-1.3;1.3)    | >0.99      | 0(-1.3;1.3)     | >0.99      |  |
| Hemodynamic instability              | 4(1.1%)       | 6(1.7%)           | 7(2%)             | -0.6(-1.3;2.7) | 0.54       | -0.9(-1.0;3.1) | 0.37       | -0.3(-1.9;2.6)  | 0.77       |  |
| Cardio-respiratory arrest            | 2(0.5%)       | 3(0.8%)           | 2(0.6%)           | -0.3(-1.2;2.0) | 0.67       | 0(-1.4;1.6)(   | >0.99      | 0.3(-1.3;2.0)   | >0.99      |  |
| Neonates with CO <sub>2</sub> > 50mm | Hg before o   | r in the 24h afte | er the extubation |                |            |                |            |                 |            |  |
|                                      | NCPAP         | NIPPV             | NHFOV             | NCPAP - NIPPV  |            | NCPAP - NHFO   | V          | NIPPV - NHFOV   |            |  |
|                                      | (N=123)       | (N=94)            | (N=90)            | Difference     | Post-hoc p | Difference     | Post-hoc p | Difference      | Post-hoc p |  |
| Severe respiratory acidosis          | 6(4.9%)       | 2(2.1%)           | 2(2.2%)           | 2.7(-3.1;8.3)  | 0.47       | 2.6(-3.4;8.2)  | 0.47       | -0.1(-5.4;5.8)  | >0.99      |  |
| Refractory hypoxemia                 | 45(36.6%<br>) | 17(18.1%)         | 16(17.8%)         | 18.5(6.5;29.4) | 0.003      | 18.8(6.6;29.7) | 0.003      | 0.3(-10.9;11.4) | >0.99      |  |
| Severe apneas                        | 11(8.9%)      | 7(7.4%)           | 4(4.4%)           | 1.5(-6.6;8.9)  | 0.69       | 4.5(-3.0;11.1) | 0.28       | 3.0(-4.5;10.6)  | 0.54       |  |
| Pulmonary hemorrhage                 | 0             | 0                 | 0                 | 0              |            | 0              |            | 0               |            |  |
| Hemodynamic instability              | 2(1.6%)       | 4(4.2%)           | 3(3.3%)           | -2.6(-2.2;8.9) | 0.41       | -1.7(-2.9;7.8) | 0.65       | 0.9(-5.6;7.5)   | >0.99      |  |
| Cardio-respiratory arrest            | 0             | 0                 | 0                 | 0              |            | 0              |            | 0               |            |  |
| Neonates with CO <sub>2</sub> ≤ 50mm | Hg before o   | r in the 24h afte | er the extubation |                |            |                |            |                 |            |  |
|                                      | NCPAP         | NIPPV             | NHFOV             | NCPAP - NIPPV  |            | NCPAP - NHFOV  | 1          | NIPPV - NHFOV   |            |  |
|                                      | (N=357)       | (N=386)           | (N=390)           | Difference     | Post-hoc p | Difference     | Post-hoc p | Difference      | Post-hoc p |  |
| Severe respiratory acidosis          | 15(4.2%)      | 6(1.5%)           | 4(1%)             | 2.6(0.2;5.4)   | 0.03       | 3.2(0.9;5.8)   | 0.009      | 0.5(-1.2;2.4)   | 0.54       |  |
| Refractory hypoxemia                 | 32(8.9%)      | 36(9.3%)          | 22(5.6%)          | -0.3(-3.9;4.5) | 0.78       | 3.3(-0.4;7.2)  | 0.10       | 3.7(0;7.5)      | 0.05       |  |
| Severe apneas                        | 5(1.4%)       | 5(1.3%)           | 5(1.3%)           | 0.1(-1.8;2.1)  | >0.99      | 0.1(-1.7;2.1)  | >0.99      | 0(-1.8;1.9)     | >0.99      |  |
| Pulmonary hemorrhage                 | 2(0.5%)       | 1(0.2%)           | 1(0.2%)           | 0.3(-0.9;1.8)  | 0.61       | 0.3(-0.9;1.8)  | 0.61       | 0(-1.2;1.2)     | >0.99      |  |
| Hemodynamic instability              | 3(0.8%)       | 3(0.8%)           | 4(1%)             | 0(-1.5;1.7)    | >0.99      | -0.2(-1.5;1.8) | >0.99      | -0.2(-1.3;1.9)  | >0.99      |  |
| Cardio-respiratory arrest            | 2(0.5%)       | 3(0.8%)           | 2(0.5%)           | -0.2(-1.3;1.7) | >0.99      | 0(-1.3;1.5)    | >0.99      | 0.2(-1.2;1.8)   | >0.99      |  |

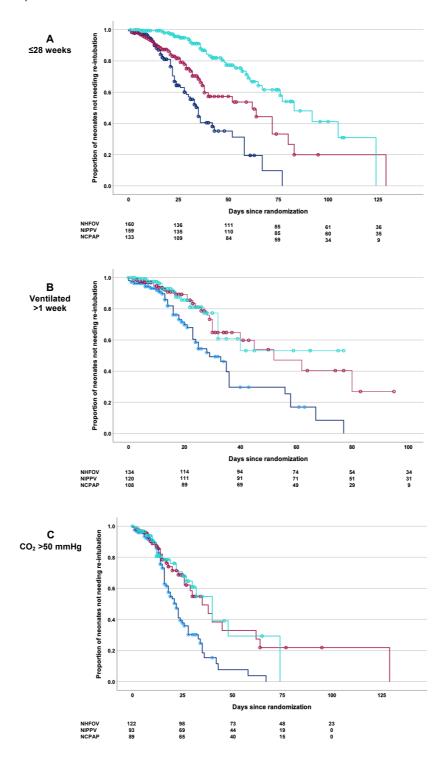
eTable 3. Interaction Analyses for All Coprimary Outcomes. Data are expressed as hazard ratio (for reintubation and early reintubations) or  $\beta$  coefficient (for duration of invasive ventilation and ventilator-free days) relative to the interaction term between the study intervention and the variable used to define subgroups, per each regression model. **Abbreviations:** CI: confidence interval; HR: hazard ratio; IMV: invasive mechanical ventilation; VFD: ventilator-free days.

|   | HR or β | 95%CI       | р      |  |  |  |  |  |  |  |
|---|---------|-------------|--------|--|--|--|--|--|--|--|
| Neonates ≤28 <sup>+6</sup> weeks' gestation |         |             |        |  |  |  |  |  |  |  |
| Duration of IMV                             | 0.09    | -1.1; 1.2   | 0.945  |  |  |  |  |  |  |  |
| Reintubations                               | 1.007   | 0.82; 1.24  | 0.950  |  |  |  |  |  |  |  |
| Early reintubations                         | 1.001   | 0.77; 1.30  | 0.995  |  |  |  |  |  |  |  |
| VFD   | 4.63    | 2.7; 10.2   | <0.001 |  |  |  |  |  |  |  |
| Neonates ventilated ≥ 1week from birth      |         |             |        |  |  |  |  |  |  |  |
| Duration of IMV                             | 1.6     | 0.04; 0.9   | 0.032  |  |  |  |  |  |  |  |
| Reintubations                               | 0.959   | 0.83; 1.1   | 0.569  |  |  |  |  |  |  |  |
| Early reintubations                         | 1.05    | 0.9; 1.23   | 0.529  |  |  |  |  |  |  |  |
| VFD   | 0.64    | -0.79;2     | 0.395  |  |  |  |  |  |  |  |
| Neonates with CO <sub>2</sub> > 50r         | nmHg    |             |        |  |  |  |  |  |  |  |
| Duration of IMV                             | -0.24   | -0.1: 0.04  | 0.367  |  |  |  |  |  |  |  |
| Reintubations                               | 1.005   | 0.98; 1.023 | 0.571  |  |  |  |  |  |  |  |
| Early reintubations                         | 1.01    | 0.99; 1.029 | 0.317  |  |  |  |  |  |  |  |
| VFD   | -0.42   | -0.39;0.05  | 0.126  |  |  |  |  |  |  |  |

eTable 4. Expected False-Positive Rates for All Coprimary Outcomes. Abbreviations: NCPAP: nasal continuous positive airway pressure; NHFOV: non-invasive high-frequency oscillation ventilation; NIPPV: noninvasive positive pressure ventilation; VFD: ventilator-free days.

| Reintubations   |  | Duration IMV   |   |  |  |  |  |
|---|--|--|---|--|--|--|--|
| Neonates ≤28 <sup>+6</sup> weeks' gestati   | on   | Neonates ≤28 <sup>+6</sup> weeks' gesta  | tion  |  |  |  |  |
| NCPAP vs NIPPV  | 0.018  | NCPAP vs NIPPV   | 0.02  |  |  |  |  |
| NCPAP vs NHFOV  | 0.007  | NCPAP vs NHFOV   | 0.01  |  |  |  |  |
| NIPPV vs NHFOV  | 0.04   | NIPPV vs NHFOV   | 0.049   |  |  |  |  |
| Neonates ventilated ≥ 1week f   | rom birth  | Neonates ventilated ≥ 1week  | from birth  |  |  |  |  |
| NCPAP vs NIPPV  | 0.008  | NCPAP vs NIPPV   | 0.008   |  |  |  |  |
| NCPAP vs NHFOV  | 0.003  | NCPAP vs NHFOV   | 0.03  |  |  |  |  |
| NIPPV vs NHFOV  | 0.04   | NIPPV vs NHFOV   | 0.03  |  |  |  |  |
| Neonates with CO <sub>2</sub> > 50mmHg  |  | Neonates with CO <sub>2</sub> > 50mmHg   |   |  |  |  |  |
| NCPAP vs NIPPV  | 0.014  | NCPAP vs NIPPV   | 0.04  |  |  |  |  |
| NCPAP vs NHFOV  | 0.004  | NCPAP vs NHFOV   | 0.04  |  |  |  |  |
| NIPPV vs NHFOV  | 0.04   | NIPPV vs NHFOV   | 0.04  |  |  |  |  |
| Early reintubations   |  | VFD  |   |  |  |  |  |
|   |  |  |   |  |  |  |  |
| Neonates ≤28 <sup>+6</sup> weeks' gestati   | on   | Neonates ≤28 <sup>+6</sup> weeks' gesta  | tion  |  |  |  |  |
| Neonates ≤28 <sup>+6</sup> weeks' gestati<br>NCPAP vs NIPPV   | on<br>0.008  | NCPAP vs NIPPV   | <b>tion</b><br>0.03   |  |  |  |  |
|   |  |  |   |  |  |  |  |
| NCPAP vs NIPPV  | 0.008  | NCPAP vs NIPPV   | 0.03  |  |  |  |  |
| NCPAP vs NIPPV<br>NCPAP vs NHFOV  | 0.008<br>0.005<br>0.04   | NCPAP vs NIPPV<br>NCPAP vs NHFOV   | 0.03<br>0.049<br>0.04   |  |  |  |  |
| NCPAP vs NIPPV<br>NCPAP vs NHFOV<br>NIPPV vs NHFOV  | 0.008<br>0.005<br>0.04   | NCPAP vs NIPPV<br>NCPAP vs NHFOV<br>NIPPV vs NHFOV   | 0.03<br>0.049<br>0.04   |  |  |  |  |
| NCPAP vs NIPPV NCPAP vs NHFOV NIPPV vs NHFOV Neonates ventilated ≥ 1week f  | 0.008<br>0.005<br>0.04<br>rom birth                            | NCPAP vs NIPPV NCPAP vs NHFOV NIPPV vs NHFOV Neonates ventilated ≥ 1week   | 0.03<br>0.049<br>0.04<br>from birth                           |  |  |  |  |
| NCPAP vs NIPPV NCPAP vs NHFOV NIPPV vs NHFOV Neonates ventilated ≥ 1week f NCPAP vs NIPPV   | 0.008<br>0.005<br>0.04<br>rom birth<br>0.007                   | NCPAP vs NIPPV NCPAP vs NHFOV NIPPV vs NHFOV Neonates ventilated ≥ 1week NCPAP vs NIPPV  | 0.03<br>0.049<br>0.04<br><b>from birth</b><br>0.049           |  |  |  |  |
| NCPAP vs NIPPV NCPAP vs NHFOV NIPPV vs NHFOV  Neonates ventilated ≥ 1week f NCPAP vs NIPPV NCPAP vs NHFOV   | 0.008<br>0.005<br>0.04<br>rom birth<br>0.007<br>0.006<br>0.049 | NCPAP vs NIPPV NCPAP vs NHFOV NIPPV vs NHFOV Neonates ventilated ≥ 1week NCPAP vs NIPPV NCPAP vs NHFOV   | 0.03<br>0.049<br>0.04<br>from birth<br>0.049<br>0.04<br>0.038 |  |  |  |  |
| NCPAP vs NIPPV NCPAP vs NHFOV NIPPV vs NHFOV  Neonates ventilated ≥ 1week f NCPAP vs NIPPV NCPAP vs NHFOV NIPPV vs NHFOV                            | 0.008<br>0.005<br>0.04<br>rom birth<br>0.007<br>0.006<br>0.049 | NCPAP vs NIPPV NCPAP vs NHFOV NIPPV vs NHFOV  Neonates ventilated ≥ 1week NCPAP vs NIPPV NCPAP vs NHFOV NIPPV vs NHFOV                           | 0.03<br>0.049<br>0.04<br>from birth<br>0.049<br>0.04<br>0.038 |  |  |  |  |
| NCPAP vs NIPPV NCPAP vs NHFOV NIPPV vs NHFOV  Neonates ventilated ≥ 1week f NCPAP vs NIPPV NCPAP vs NHFOV NIPPV vs NHFOV Neonates with CO₂ > 50mmHg | 0.008<br>0.005<br>0.04<br>rom birth<br>0.007<br>0.006<br>0.049 | NCPAP vs NIPPV NCPAP vs NHFOV NIPPV vs NHFOV  Neonates ventilated ≥ 1week NCPAP vs NIPPV NCPAP vs NHFOV NIPPV vs NHFOV Neonates with CO₂ > 50mmH | 0.03<br>0.049<br>0.04<br>from birth<br>0.049<br>0.04<br>0.038 |  |  |  |  |

**eFigure 2. Kaplan-Meier Analysis for Reintubations.** Panel A, B and C show subgroup analysis for neonates ≤28 weeks' gestation, invasively ventilated for > 1 week and in those with CO₂ > 50mmHg, respectively. Blue, violet and turquoise lines depict NCPAP, NIPPV and NHFOV arms, respectively. Curves are different at Logrank test (p<0.001). Open circles represent censored cases. **Abbreviations**: NCPAP: nasal continuous positive airway pressure; NHFOV: non-invasive high-frequency oscillation ventilation; NIPPV: noninvasive positive pressure ventilation.



# eFigure 3. Secondary Outcomes: Use of Postnatal Steroids (A), In-Hospital

**Mortality (B) and BPD/Mortality (C).** Subgroups of interest are highlighted with a grey background, alternate subgroups have no background. Data are shown as risk difference and 95% confidence interval and illustrated as Forrest plots per each subgroup. Squares and lines indicate the mean differences and their 95% confidence interval, respectively. Square size is proportional to the subgroup numerosity. Blue and green lines indicate comparisons significantly in favor of NIPPV and NHFOV, respectively (*p*-values for significant comparisons in subgroups of interest are as follows, **Panel C**: difference in risk of BPD/mortality composite endpoint in neonates with a gestational age ≤28 weeks: NHFOV vs NCPAP *p*=0.03). **Abbreviations**: BPD: bronchopulmonary dysplasia; Cl: confidence interval; NCPAP: nasal continuous positive airway pressure; NHFOV: non-invasive high-frequency oscillation ventilation; NIPPV: noninvasive positive pressure ventilation.



| A                                |                            |                                  |                                  |      |       |   |        |       |     |
|----------------------------------|----------------------------|----------------------------------|----------------------------------|------|-------|---|--------|-------|-----|
| Comparisons                      | Risk Difference<br>(95%CI) | Steroids<br>-treated<br>neonates | Steroids<br>-treated<br>neonates |      |       | I |        |       |     |
| NCPAP vs NIPPV (<=28W)           | 0.103 (-0.003, 0.209)      | 49/134                           | 42/160                           |      |       | - |        |       |     |
| NCPAP vs NHFOV (<=28W)           | 0.092 (-0.014, 0.199)      | 49/134                           | 44/161                           |      |       | _ |        |       |     |
| NIPPV vs NHFOV (<=28W)           | -0.011 (-0.108, 0.086)     | 42/160                           | 44/161                           |      |       |   |        |       | _   |
| ICPAP vs NIPPV (>28W)            | 0.032 (-0.018, 0.082)      | 49/346                           | 35/320                           |      |       | _ | -      |       | _   |
| ICPAP vs NHFOV (>28W)            | 0.082 (0.037, 0.127)       | 49/346                           | 19/319                           |      |       |   |        |       |     |
| IIPPV vs NHFOV (>28W)            | 0.050 (0.007, 0.093)       | 35/320                           | 19/319                           |      |       | - |        |       | _   |
| ICPAP vs NIPPV (Ventilated >=1W) | 0.039 (-0.079, 0.157)      | 37/110                           | 39/131                           |      |       | _ |        |       |     |
| CPAP vs NHFOV (Ventilated >=1W)  | 0.135 (0.023, 0.246)       | 37/110                           | 27/134                           |      |       |   |        |       |     |
| IPPV vs NHFOV (Ventilated >=1W)  | 0.096 (-0.007, 0.200)      | 39/131                           | 27/134                           |      |       | + |        |       |     |
| CPAP vs NIPPV (Ventilated <1W)   | 0.056 (0.006, 0.106)       | 61/370                           | 38/349                           |      |       |   | _      |       |     |
| CPAP vs NHFOV (Ventilated <1W)   | 0.061 (0.011, 0.110)       | 61/370                           | 36/346                           |      |       |   | _      |       |     |
| PPV vs NHFOV (Ventilated <1W)    | 0.005 (-0.041, 0.051)      | 38/349                           | 36/346                           |      | _     |   |        |       |     |
| CPAP vs NIPPV (CO2 >50 mmHg)     | 0.072 (-0.047, 0.192)      | 39/123                           | 23/94                            |      |       | _ | -      | -     |     |
| CPAP vs NHFOV (CO2 >50 mmHg)     | 0.150 (0.038, 0.263)       | 39/123                           | 15/90                            |      |       |   |        | _     |     |
| PPV vs NHFOV (CO2 >50 mmHg)      | 0.078 (-0.038, 0.194)      | 23/94                            | 15/90                            |      | _     | _ |        | •     |     |
| CPAP vs NIPPV (CO2 <=50 mmHg)    | 0.025 (-0.026, 0.077)      | 59/357                           | 54/386                           |      | -     |   | -      | -     |     |
| CPAP vs NHFOV (CO2 <=50 mmHg)    | 0.042 (-0.008, 0.093)      | 59/357                           | 48/390                           |      |       | - | -      | —     |     |
| NIPPV vs NHFOV (CO2 <=50 mmHg)   | 0.017 (-0.031, 0.064)      | 54/386                           | 48/390                           |      | -     |   |        |       |     |
|                                  |                            |                                  |                                  |      |       |   |        | _     |     |
|                                  |                            |                                  |                                  | -0.1 | -0.05 | 0 | 0.05   |       | 0.1 |
| 1                                |                            |                                  |                                  |      |       |   | Risk I | Diffe | re  |

В

| Comparisons                      | Risk Difference<br>(95%CI) | Deaths | Deaths | ths                           |
|----------------------------------|----------------------------|--------|--------|-------------------------------|
| NCPAP vs NIPPV (<=28W)           | 0.002 (-0.024, 0.029)      | 2/134  | 2/160  | 60                            |
| NCPAP vs NHFOV (<=28W)           | -0.016 (-0.050, 0.018)     | 2/134  | 5/161  | 61 -                          |
| NIPPV vs NHFOV (<=28W)           | -0.019 (-0.050, 0.013)     | 2/160  | 5/161  | 61                            |
| NCPAP vs NIPPV (>28W)            | 0.002 (-0.011, 0.015)      | 3/346  | 2/320  | 20                            |
| NCPAP vs NHFOV (>28W)            | -0.001 (-0.015, 0.014)     | 3/346  | 3/319  | <u></u>                       |
| NIPPV vs NHFOV (>28W)            | -0.003 (-0.017, 0.011)     | 2/320  | 3/319  | 19 —                          |
| NCPAP vs NIPPV (Ventilated >=1W) | 0.011 (-0.019, 0.040)      | 2/110  | 1/131  | 31                            |
| NCPAP vs NHFOV (Ventilated >=1W) | -0.012 (-0.050, 0.026)     | 2/110  | 4/134  | 34                            |
| NIPPV vs NHFOV (Ventilated >=1W) | -0.022 (-0.055, 0.010)     | 1/131  | 4/134  | 34                            |
| NCPAP vs NIPPV (Ventilated <1W)  | -0.000 (-0.014, 0.013)     | 3/370  | 3/349  | 49 —                          |
| NCPAP vs NHFOV (Ventilated <1W)  | -0.003 (-0.018, 0.011)     | 3/370  | 4/346  | 46                            |
| NIPPV vs NHFOV (Ventilated <1W)  | -0.003 (-0.018, 0.012)     | 3/349  | 4/346  | 46                            |
| NCPAP vs NIPPV (CO2 >50 mmHg)    | -0.016 (-0.058, 0.026)     | 2/123  | 3/94   | 4                             |
| NCPAP vs NHFOV (CO2 >50 mmHg)    | -0.017 (-0.060, 0.026)     | 2/123  | 3/90   | 0 -                           |
| NIPPV vs NHFOV (CO2 >50 mmHg)    | -0.001 (-0.053, 0.050)     | 3/94   | 3/90   | 0 -                           |
| NCPAP vs NIPPV (CO2 <=50 mmHg)   | 0.006 (-0.005, 0.017)      | 3/357  | 1/386  | 86                            |
| NCPAP vs NHFOV (CO2 <=50 mmHg)   | -0.004 (-0.019, 0.010)     | 3/357  | 5/390  | 90                            |
| NIPPV vs NHFOV (CO2 <=50 mmHg)   | -0.010 (-0.022, 0.002)     | 1/386  | 5/390  | 90                            |
|                                  | •                          |        |        | <del> </del>                  |
|                                  |                            |        |        | -0.06 -0.04 -0.02 0 0.02 0.04 |
|                                  |                            |        |        | Risk Difference               |

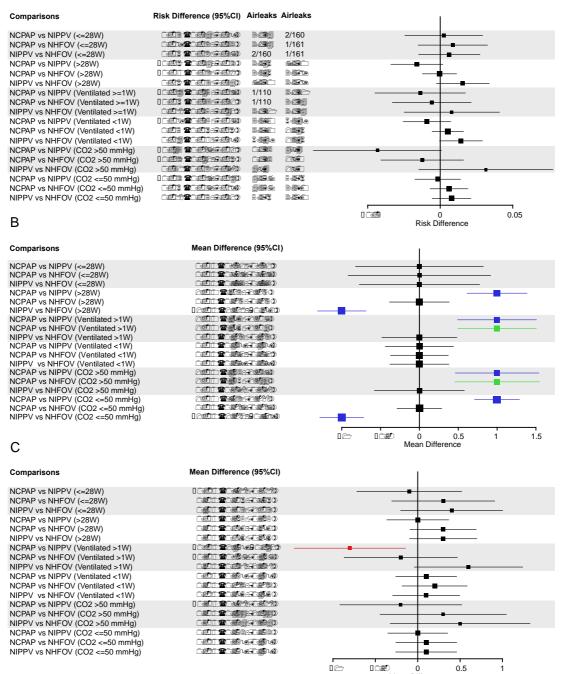
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| Comparisons                      | Risk Difference<br>(95%CI) | BPD/<br>Deaths | BPD/<br>Deaths |       |      |       | ı            |              |     |      |     |
|----------------------------------|----------------------------|----------------|----------------|-------|------|-------|--------------|--------------|-----|------|-----|
| NCPAP vs NIPPV (<=28W)           | 0.091 ( -0.012, 0.195)     | 101/134        | 106/160        |       |      |       | _            |              | _   |      |     |
| NCPAP vs NHFOV (<=28W)           | 0.120 (0.016, 0.224)       | 101/134        | 102/161        |       |      |       | -   -        |              |     |      |     |
| NIPPV vs NHFOV (<=28W)           | 0.029 ( -0.075, 0.133)     | 106/160        | 102/161        |       |      |       |              | _            |     | _    |     |
| NCPAP vs NIPPV (>28W)            | 0.004 ( -0.062, 0.070)     | 88/346         | 80/320         |       |      |       |              |              |     |      |     |
| NCPAP vs NHFOV (>28W)            | 0.038 ( -0.026, 0.102)     | 88/346         | 69/319         |       |      | -     | _            | _            |     |      |     |
| NIPPV vs NHFOV (>28W)            | 0.034 ( -0.032, 0.099)     | 80/320         | 69/319         |       |      | _     | -            | -            |     |      |     |
| NCPAP vs NIPPV (Ventilated >=1W) | 0.040 ( -0.086, 0.165)     | 64/110         | 71/131         |       | -    |       |              |              |     |      |     |
| NCPAP vs NHFOV (Ventilated >=1W) | 0.097 ( -0.028, 0.222)     | 64/110         | 65/134         |       |      | -     |              |              | -   |      |     |
| NIPPV vs NHFOV (Ventilated >=1W) | 0.057 ( -0.063, 0.177)     | 71/131         | 65/134         |       |      |       |              |              |     |      |     |
| NCPAP vs NIPPV (Ventilated <1W)  | 0.008 ( -0.061, 0.077)     | 125/370        | 115/349        |       |      |       |              |              |     |      |     |
| NCPAP vs NHFOV (Ventilated <1W)  | 0.031 ( -0.037, 0.100)     | 125/370        | 106/346        |       |      | _     | _            | -            |     |      |     |
| NIPPV vs NHFOV (Ventilated <1W)  | 0.023 ( -0.046, 0.092)     | 115/349        | 106/346        |       |      | _     |              | -            | _   |      |     |
| NCPAP vs NIPPV (CO2 >50 mmHg)    | 0.015 ( -0.120, 0.149)     | 62/123         | 46/94          |       |      |       |              |              |     |      |     |
| NCPAP vs NHFOV (CO2 >50 mmHg)    | 0.004 ( -0.132, 0.140)     | 62/123         | 45/90          | -     |      |       | -            |              |     | _    |     |
| NIPPV vs NHFOV (CO2 >50 mmHg)    | -0.011 ( -0.155, 0.134)    | 46/94          | 45/90          |       |      |       | -            |              |     | _    |     |
| NCPAP vs NIPPV (CO2 <=50 mmHg)   | -0.007 ( -0.076, 0.062)    | 127/357        | 140/386        |       |      |       | -            |              |     |      |     |
| NCPAP vs NHFOV (CO2 <=50 mmHg)   | 0.033 ( -0.035, 0.101)     | 127/357        | 126/390        |       |      | _     | -            | -            |     |      |     |
| NIPPV vs NHFOV (CO2 <=50 mmHg)   | 0.040 ( -0.027, 0.106)     | 140/386        | 126/390        |       |      | -     | -            | -            |     |      |     |
|                                  |                            |                |                | 0.45  | 0.4  | 0.05  | <del> </del> | 0.05         | 1   | 0.45 |     |
|                                  |                            |                |                | -0.15 | -0.1 | -0.05 | 0            | 0.05         | 0.1 | 0.15 | 0.2 |
|                                  |                            |                |                |       |      |       | Risk         | c Difference | е   |      |     |

## eFigure 4. Secondary Outcomes: Airleaks (A), Number of Apneas/Week (B) and

**PIPP Score (C).** Subgroups of interest are highlighted with a grey background, alternate subgroups have no background. PIPP is a dimensionless variable. Data are shown as risk difference and 95% confidence interval (for airleaks) and as mean difference and 95% confidence interval (for the number of apneas/week and the PIPP score). Data are illustrated as Forrest plots per each subgroup. Squares and lines indicate the mean differences and their 95% confidence interval, respectively. Square size is proportional to the subgroup numerosity. Blue, green and red lines indicate comparisons significantly in favor of NIPPV, NHFOV and NCPAP, respectively (*p*-values for significant comparisons in subgroups of interest are as follows, **Panel B**: difference in mean number of apneas/week in neonates invasively ventilated for at least 1 week: NIPPV vs NCPAP *p*=0.03, NHFOV vs NCPAP *p*=0.03; difference in mean number of apneas/week in neonates with CO<sub>2</sub> >50 mmHg before or in the 24h after the extubation: NIPPV vs NCPAP *p*=0.03, NHFOV vs NCPAP *p*=0.03). **Abbreviations**: CI: confidence interval; NCPAP: nasal continuous positive airway pressure; NHFOV: non-invasive high-frequency oscillation ventilation; NIPPV: noninvasive positive pressure ventilation; PIPP: premature infant pain profile.

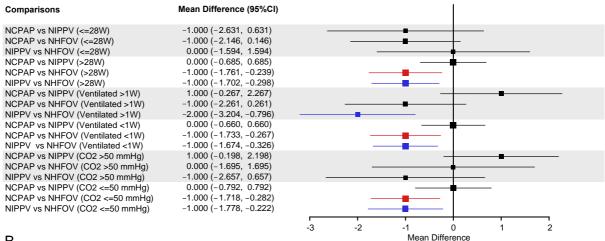




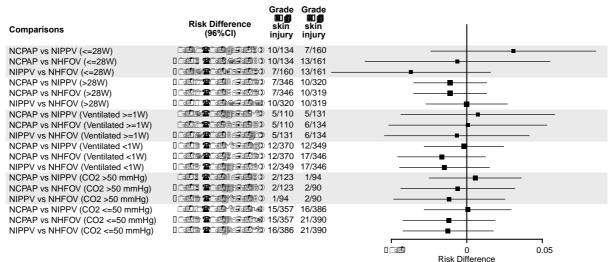
## eFigure 5. Secondary Outcomes: Weekly Weight Gain (A) and Severe Nasal Skin

Injury (B). Subgroups of interest are highlighted with a grey background, alternate subgroups have no background. Weekly weight gain is expressed in grams; severe nasal skin injury was diagnosed if classified as grade III-IV using a dedicated dimensionless score; more details in the trial protocol). Data are shown as mean difference and 95% confidence interval (for weekly weight gain) and as risk difference and 95% confidence interval (for severe nasal skin injury); Data are illustrated as Forrest plots per each subgroup. Squares and lines indicate the mean differences and their 95% confidence interval, respectively. Square size is proportional to the subgroup numerosity. Blue and red lines indicate comparisons significantly in favor of NIPPV and NCPAP, respectively. Abbreviations: CI: confidence interval; NCPAP: nasal continuous positive airway pressure; NHFOV: non-invasive high-frequency oscillation ventilation; NIPPV: noninvasive positive pressure ventilation.



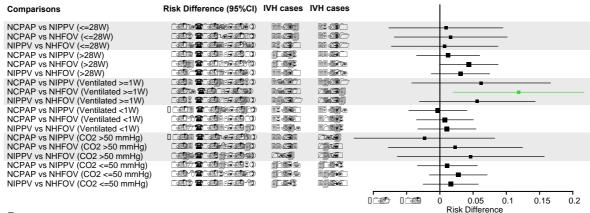




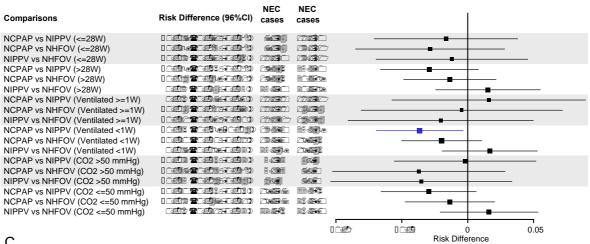


eFigure 6. Secondary Outcomes: IVH (A), NEC (B) and ROP (C). Subgroups of interest are highlighted with a grey background, alternate subgroups have no background. IVH were considered if  $>2^{nd}$  grade, NEC were considered if  $\ge 2^{nd}$  stage and ROP were considered if  $>2^{nd}$  stage (more details in the trial protocol). Data are shown as risk difference and 95% confidence interval. Data are illustrated as Forrest plots per each subgroup. Squares and lines indicate the mean differences and their 95% confidence interval, respectively. Square size is proportional to the subgroup numerosity. Blue and green lines indicate comparisons significantly in favor of NIPPV and NHFOV, respectively. Abbreviations: ČI: confidence interval; IVH: intra-ventricular hemorrhage; NEC: necrotizing entero-colitis; NCPAP: nasal continuous positive airway pressure; NHFOV: non-invasive high-frequency oscillation ventilation; NIPPV. noninvasive positive pressure ventilation; ROP: retinopathy of prematurity.

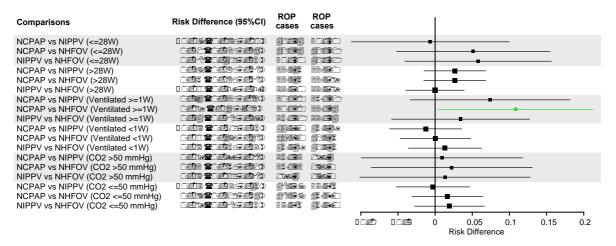




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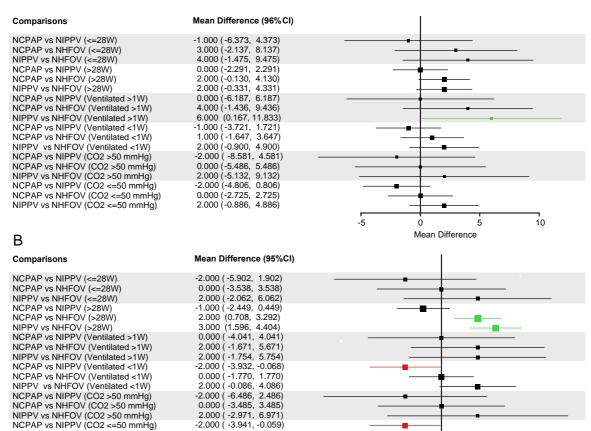
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## eFigure 7. Secondary Outcomes: Duration of Oxygen Supplementation (A) and of

**Study Intervention (B).** Subgroups of interest are highlighted with a grey background, alternate subgroups have no background. Both outcomes are measured in days. Data are shown as mean difference and 95% confidence interval. Data are illustrated as Forrest plots per each subgroup. Squares and lines indicate the mean differences and their 95% confidence interval, respectively. Square size is proportional to the subgroup numerosity. Green and red lines indicate comparisons significantly in favor of NHFOV and NCPAP, respectively. **Abbreviations**: Cl: confidence interval; NCPAP: nasal continuous positive airway pressure; NHFOV: non-invasive high-frequency oscillation ventilation; NIPPV: noninvasive positive pressure ventilation.





Mean Difference

-2.000 ( -3.941, -0.059) 1.000 ( -0.866, 2.866) 3.000 (1.099, 4.901)

NCPAP vs NHFOV (CO2 <=50 mmHg) NIPPV vs NHFOV (CO2 <=50 mmHq)