#### 1.1 Death

|  | LIST                    | Г        | Contr         | ol                    |                    | Risk Ratio          | Risk Ratio                                 |
|--|-------------------------|----------|---------------|-----------------------|--------------------|---------------------|--|
| Study or Subgroup                      | Events                  | Total    | <b>Events</b> | Total                 | Weight             | M-H, Random, 95% CI | M-H, Random, 95% CI                        |
| 1.1.1 vs InSurE                        |                         |          |               |                       |                    |                     |  |
| Kanmaz 2013                            | 16                      | 100      | 13            | 100                   | 32.3%              | 1.23 [0.63, 2.42]   | <del>-</del>                               |
| Mirnia 2013                            | 2                       | 66       | 11            | 70                    | 12.3%              | 0.19 [0.04, 0.84]   |  |
| Mohammadizadeh 2015                    | 1                       | 19       | 3             | 19                    | 6.3%               | 0.33 [0.04, 2.93]   | <del></del>                                |
| Bao 2015                               | 1                       | 47       | 0             | 43                    | 3.1%               | 2.75 [0.12, 65.76]  |  |
| Subtotal (95% CI)                      |                         | 232      |               | 232                   | 54.0%              | 0.63 [0.19, 2.04]   |  |
| Total events                           | 20                      |          | 27            |                       |                    |                     |  |
| Heterogeneity: Tau <sup>2</sup> = 0.73 | 3; Chi <sup>2</sup> = 6 | 5.50, df | = 3 (P = 0)   | 0.09); l <sup>2</sup> | <sup>2</sup> = 54% |                     |  |
| Test for overall effect: Z =           | 0.78 (P =               | 0.44)    |               |                       |                    |                     |  |
| 1.1.2 vs CPAP                          |                         |          |               |                       |                    |                     |  |
| Göpel 2011                             | 7                       | 108      | 5             | 112                   | 18.3%              | 1.45 [0.48, 4.44]   | <del></del>                                |
| Subtotal (95% CI)                      |                         | 108      |               | 112                   | 18.3%              | 1.45 [0.48, 4.44]   |  |
| Total events                           | 7                       |          | 5             |                       |                    |                     |  |
| Heterogeneity: Not applica             | ıble                    |          |               |                       |                    |                     |  |
| Test for overall effect: Z =           | 0.65 (P =               | 0.51)    |               |                       |                    |                     |  |
| 1.1.3 vs MV and surf                   |                         |          |               |                       |                    |                     |  |
| Kribs 2015                             | 10                      | 107      | 12            | 104                   | 27.7%              | 0.81 [0.37, 1.79]   | <del></del>                                |
| Subtotal (95% CI)                      |                         | 107      |               | 104                   | 27.7%              | 0.81 [0.37, 1.79]   | •  |
| Total events                           | 10                      |          | 12            |                       |                    |                     |  |
| Heterogeneity: Not applica             | able                    |          |               |                       |                    |                     |  |
| Test for overall effect: Z =           | 0.52 (P =               | 0.60)    |               |                       |                    |                     |  |
| Total (95% CI)                         |                         | 447      |               | 448                   | 100.0%             | 0.85 [0.48, 1.52]   | •  |
| Total events                           | 37                      |          | 44            |                       |                    |                     |  |
| Heterogeneity: Tau <sup>2</sup> = 0.15 | 5; Chi² = 7             | .22, df  | = 5 (P = 0    | 0.21); l²             | 2 = 31%            |                     |  |
| Test for overall effect: Z =           |                         |          | `             | ,.                    |                    |                     | 0.01 0.1 1 10 Favours LIST Favours control |
| Test for subgroup difference           | •                       | ,        | df = 2 (P     | = 0.57)               | $I^2 = 0\%$        |                     | Favours LIST Favours CONTR                 |
| 3 1                                    |                         | -,       | ν.            | /                     | ,                  |                     |  |

LIST: Less invasive surfactant therapy InSurE: Intubation- surfactant- extubation

MV and surf: mechanical ventilation and surfactant

# 1.2 BPD at 36 weeks, all patients

|  | LIS1        | -       | Contr       | ol                    |                   | Risk Ratio          | Risk Ratio                |
|--|-------------|---------|-------------|-----------------------|-------------------|---------------------|---------------------------|
| Study or Subgroup                      | Events      | Total   | Events      | Total                 | Weight            | M-H, Random, 95% CI | M-H, Random, 95% CI       |
| 1.2.1 vs InSurE                        |             |         |             |                       |                   |                     |                           |
| Kanmaz 2013                            | 9           | 100     | 17          | 100                   | 18.4%             | 0.53 [0.25, 1.13]   | <del></del>               |
| Mirnia 2013                            | 5           | 66      | 5           | 70                    | 7.4%              | 1.06 [0.32, 3.50]   | <del></del>               |
| Mohammadizadeh 2015                    | 3           | 19      | 4           | 19                    | 5.8%              | 0.75 [0.19, 2.91]   | <del></del>               |
| Bao 2015                               | 1           | 47      | 1           | 43                    | 1.4%              | 0.91 [0.06, 14.18]  |                           |
| Subtotal (95% CI)                      |             | 232     |             | 232                   | 32.9%             | 0.67 [0.38, 1.19]   |                           |
| Total events                           | 18          |         | 27          |                       |                   |                     |                           |
| Heterogeneity: Tau <sup>2</sup> = 0.00 | ); Chi² = 1 | .02, df | = 3 (P = 0) | 0.80); l <sup>2</sup> | $^{2} = 0\%$      |                     |                           |
| Test for overall effect: Z =           | 1.37 (P =   | 0.17)   |             |                       |                   |                     |                           |
| 1.2.2 vs CPAP                          |             |         |             |                       |                   |                     |                           |
| Göpel 2011                             | 8           | 108     | 14          | 112                   | 15.4%             | 0.59 [0.26, 1.36]   | <del></del>               |
| Subtotal (95% CI)                      |             | 108     |             | 112                   | 15.4%             | 0.59 [0.26, 1.36]   |                           |
| Total events                           | 8           |         | 14          |                       |                   |                     |                           |
| Heterogeneity: Not applica             | able        |         |             |                       |                   |                     |                           |
| Test for overall effect: Z =           | 1.24 (P =   | 0.22)   |             |                       |                   |                     |                           |
| 1.2.3 vs MV and surf                   |             |         |             |                       |                   |                     |                           |
| Kribs 2015                             | 25          | 107     | 31          | 104                   | 51.6%             | 0.78 [0.50, 1.23]   | -                         |
| Subtotal (95% CI)                      |             | 107     |             | 104                   | 51.6%             | 0.78 [0.50, 1.23]   | •                         |
| Total events                           | 25          |         | 31          |                       |                   |                     |                           |
| Heterogeneity: Not applica             | able        |         |             |                       |                   |                     |                           |
| Test for overall effect: Z =           | 1.05 (P =   | 0.29)   |             |                       |                   |                     |                           |
| Total (95% CI)                         |             | 447     |             | 448                   | 100.0%            | 0.71 [0.52, 0.99]   | •                         |
| Total events                           | 51          |         | 72          |                       |                   | - · · · · · · · ·   |                           |
| Heterogeneity: Tau <sup>2</sup> = 0.00 | ); Chi² = 1 | .42, df | = 5 (P = (  | ).92); l²             | <sup>2</sup> = 0% |                     |                           |
| Test for overall effect: Z =           |             |         | - (         | . ,, .                |                   |                     | 0.01 0.1 1 10             |
| Test for subgroup difference           | ,           | ,       | df = 2 (P   | = 0.82)               | $I^2 = 0\%$       |                     | Favours LIST Favours cont |

# 1.3 BPD at 36 weeks, survivors

|  | LIST                   | -       | Contr       | ol        |              | Risk Ratio          | Risk Ratio                               |
|--|------------------------|---------|-------------|-----------|--------------|---------------------|--|
| Study or Subgroup                      | Events                 | Total   | Events      | Total     | Weight       | M-H, Random, 95% CI | M-H, Random, 95% CI                      |
| 1.3.1 vs InSurE                        |                        |         |             |           |              |                     |  |
| Kanmaz 2013                            | 9                      | 84      | 17          | 87        | 18.2%        | 0.55 [0.26, 1.16]   | <del></del>                              |
| Mirnia 2013                            | 5                      | 64      | 5           | 59        | 7.3%         | 0.92 [0.28, 3.02]   | <del></del>                              |
| Mohammadizadeh 2015                    | 3                      | 18      | 4           | 16        | 5.7%         | 0.67 [0.18, 2.54]   | <del></del>                              |
| Bao 2015                               | 1                      | 46      | 1           | 43        | 1.4%         | 0.93 [0.06, 14.48]  |  |
| Subtotal (95% CI)                      |                        | 212     |             | 205       | 32.6%        | 0.65 [0.37, 1.14]   | •  |
| Total events                           | 18                     |         | 27          |           |              |                     |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00 | ; $Chi^2 = 0$          | .60, df | = 3 (P = 0) | 0.90); l² | $^{2} = 0\%$ |                     |  |
| Test for overall effect: Z = 1         | 1.50 (P =              | 0.13)   |             |           |              |                     |  |
| 1.3.2 vs CPAP                          |                        |         |             |           |              |                     |  |
| Göpel 2011                             | 8                      | 101     | 14          | 107       | 15.1%        | 0.61 [0.27, 1.38]   | <del></del>                              |
| Subtotal (95% CI)                      |                        | 101     |             | 107       | 15.1%        | 0.61 [0.27, 1.38]   |  |
| Total events                           | 8                      |         | 14          |           |              |                     |  |
| Heterogeneity: Not applical            | ble                    |         |             |           |              |                     |  |
| Test for overall effect: Z = 1         | 1.19 (P =              | 0.23)   |             |           |              |                     |  |
| 1.3.3 vs MV and SURF                   |                        |         |             |           |              |                     |  |
| Kribs 2015                             | 25                     | 97      | 31          | 92        | 52.3%        | 0.76 [0.49, 1.19]   | -  |
| Subtotal (95% CI)                      |                        | 97      |             | 92        | 52.3%        | 0.76 [0.49, 1.19]   |  |
| Total events                           | 25                     |         | 31          |           |              |                     |  |
| Heterogeneity: Not applical            | ble                    |         |             |           |              |                     |  |
| Test for overall effect: Z = 1         | 1.19 (P =              | 0.24)   |             |           |              |                     |  |
| Total (95% CI)                         |                        | 410     |             | 404       | 100.0%       | 0.70 [0.51, 0.97]   | <b>•</b>                                 |
| Total events                           | 51                     |         | 72          |           |              |                     |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00 | ; Chi <sup>2</sup> = 0 | .94, df | = 5 (P = 0  | ).97); l² | 2 = 0%       |                     |  |
| Test for overall effect: Z = 2         |                        |         | `           | ,,        |              |                     | 0.01 0.1 1 10 Favours LIST Favours contr |
| Test for subgroup difference           | `                      | ,       | df = 2 (P   | = 0.85)   | $I^2 = 0\%$  |                     | ravours LIST Favours confi               |

## 1.4 Death or BPD

|  | LIST          | -       | Contr         | ol                    |              | Risk Ratio          | Risk Ratio                                 |
|--|---------------|---------|---------------|-----------------------|--------------|---------------------|--|
| Study or Subgroup                      | <b>Events</b> | Total   | <b>Events</b> | Total                 | Weight       | M-H, Random, 95% CI | M-H, Random, 95% CI                        |
| 1.4.1 vs InSurE                        |               |         |               |                       |              |                     |  |
| Kanmaz 2013                            | 22            | 100     | 32            | 100                   | 26.2%        | 0.69 [0.43, 1.10]   | <del>-=</del> +                            |
| Mirnia 2013                            | 7             | 66      | 16            | 70                    | 8.5%         | 0.46 [0.20, 1.06]   | <del></del>                                |
| Mohammadizadeh 2015                    | 4             | 19      | 7             | 19                    | 5.2%         | 0.57 [0.20, 1.63]   | <del></del>                                |
| Bao 2015                               | 2             | 47      | 1             | 43                    | 1.0%         | 1.83 [0.17, 19.47]  | <del>-   -</del>                           |
| Subtotal (95% CI)                      |               | 232     |               | 232                   | 40.9%        | 0.63 [0.44, 0.92]   | •  |
| Total events                           | 35            |         | 56            |                       |              |                     |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00 | ); Chi² = 1   | .48, df | = 3 (P = 0)   | 0.69); l <sup>2</sup> | $^{2} = 0\%$ |                     |  |
| Test for overall effect: Z = 2         | 2.38 (P =     | 0.02)   |               |                       |              |                     |  |
| 1.4.2 vs CPAP                          |               |         |               |                       |              |                     |  |
| Göpel 2011                             | 15            | 108     | 17            | 112                   | 13.9%        | 0.92 [0.48, 1.74]   | <del>-</del>                               |
| Subtotal (95% CI)                      |               | 108     |               | 112                   | 13.9%        | 0.92 [0.48, 1.74]   | •  |
| Total events                           | 15            |         | 17            |                       |              |                     |  |
| Heterogeneity: Not applica             | ble           |         |               |                       |              |                     |  |
| Test for overall effect: Z = 0         | 0.27 (P =     | 0.79)   |               |                       |              |                     |  |
| 1.4.3 vs MV and surf                   |               |         |               |                       |              |                     |  |
| Kribs 2015                             | 35            | 107     | 43            | 104                   | 45.3%        | 0.79 [0.55, 1.13]   | -  |
| Subtotal (95% CI)                      |               | 107     |               | 104                   | 45.3%        | 0.79 [0.55, 1.13]   | •  |
| Total events                           | 35            |         | 43            |                       |              |                     |  |
| Heterogeneity: Not applica             | ble           |         |               |                       |              |                     |  |
| Test for overall effect: Z =           | 1.29 (P =     | 0.20)   |               |                       |              |                     |  |
| Total (95% CI)                         |               | 447     |               | 448                   | 100.0%       | 0.74 [0.58, 0.94]   | <b>•</b>                                   |
| Total events                           | 85            |         | 116           |                       |              | -                   |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00 | ; Chi² = 2    | .69, df | = 5 (P = 0    | ).75); l²             | 2 = 0%       |                     |  |
| Test for overall effect: Z = 2         |               |         | `             | ,,                    |              |                     | 0.01 0.1 1 10 Favours LIST Favours control |
| Test for subgroup difference           | `             | ,       | df = 2 (P     | = 0.55)               | $I^2 = 0\%$  |                     | ravours LIST ravours contr                 |

# 1.5 Early MV (by 72H)

|  | LIS1       | Г                | Contr      | ol               |                      | Risk Ratio                                     | Risk Ratio                  |
|--|------------|------------------|------------|------------------|----------------------|--|-----------------------------|
| Study or Subgroup                        | Events     | Total            | Events     | Total            | Weight               | M-H, Random, 95% CI                            | M-H, Random, 95% CI         |
| 1.5.1 vs InSurE                          |            |                  |            |                  |                      |  |                             |
| Kanmaz 2013                              | 30         | 100              | 45         | 100              | 38.6%                | 0.67 [0.46, 0.96]                              | -                           |
| Mirnia 2013                              | 13         | 66               | 16         | 70               | 12.5%                | 0.86 [0.45, 1.65]                              | <del>-</del>                |
| Bao 2015                                 | 8          | 47               | 10         | 43               | 7.6%                 | 0.73 [0.32, 1.68]                              | <del> -</del>               |
| Mohammadizadeh 2015<br>Subtotal (95% CI) | 2          | 19<br><b>232</b> | 3          | 19<br><b>232</b> | 1.9%<br><b>60.5%</b> | 0.67 [0.13, 3.55]<br><b>0.71 [0.53, 0.96</b> ] | •                           |
| Total events                             | 53         |                  | 74         |                  | 001070               | [0.00, 0.00]                                   | •                           |
| Heterogeneity: Tau <sup>2</sup> = 0.00   |            | 47 df            |            | ) 93)- 12        | <sup>2</sup> = 0%    |  |                             |
| Test for overall effect: $Z = 2$         |            |                  | <b>O</b> ( | 3.00), 1         | 0 70                 |  |                             |
|  | (.         | 0.02)            |            |                  |                      |  |                             |
| 1.5.2 vs CPAP                            |            |                  |            |                  |                      |  |                             |
| Göpel 2011                               | 30         | 108              | 51         | 112              | 39.5%                | 0.61 [0.42, 0.88]                              | -                           |
| Subtotal (95% CI)                        |            | 108              |            | 112              | 39.5%                | 0.61 [0.42, 0.88]                              | •                           |
| Total events                             | 30         |                  | 51         |                  |                      |  |                             |
| Heterogeneity: Not applica               | ble        |                  |            |                  |                      |  |                             |
| Test for overall effect: Z = 2           | 2.65 (P =  | 0.008)           |            |                  |                      |  |                             |
| 1.5.3 vs MV and surf                     |            |                  |            |                  |                      |  |                             |
| Kribs 2015                               | 0          | 0                | 0          | 0                |                      | Not estimable                                  |                             |
| Subtotal (95% CI)                        |            | 0                |            | 0                |                      | Not estimable                                  |                             |
| Total events                             | 0          |                  | 0          |                  |                      |  |                             |
| Heterogeneity: Not applica               | ble        |                  |            |                  |                      |  |                             |
| Test for overall effect: Not             | applicable | Э                |            |                  |                      |  |                             |
| Total (95% CI)                           |            | 340              |            | 344              | 100.0%               | 0.67 [0.53, 0.84]                              | <b>•</b>                    |
| Total events                             | 83         |                  | 125        |                  |                      |  |                             |
| Heterogeneity: Tau <sup>2</sup> = 0.00   |            |                  |            |                  |                      |  |                             |
| Test for overall effect: Z = 3           |            | 0.01 0.1 1 10    |            |                  |                      |  |                             |
| Test for subgroup difference             | `          |                  | ,          | = 0.52)          | $I^2 = 0\%$          |  | Favours LIST Favours contro |

Kribs 2015 not included: early mechanical ventilation mandatory for control group.

## 1.6 Any MV

|                                   | LIST              |                   | Contr         | ol                |                        | Risk Ratio                                    | Risk Ratio                    |
|-----------------------------------|-------------------|-------------------|---------------|-------------------|------------------------|---|-------------------------------|
| Study or Subgroup                 | <b>Events</b>     | Total             | <b>Events</b> | Total             | Weight                 | M-H, Random, 95% CI                           | M-H, Random, 95% CI           |
| 1.6.1 vs InSurE                   |                   |                   |               |                   |                        |   |                               |
| Kanmaz 2013<br>Subtotal (95% CI)  | 40                | 100<br><b>100</b> | 49            | 100<br><b>100</b> | 30.2%<br><b>30.2%</b>  | 0.82 [0.60, 1.12]<br><b>0.82 [0.60, 1.12]</b> | •                             |
| Total events                      | 40                |                   | 49            |                   |                        |   |                               |
| Heterogeneity: Not app            | olicable          |                   |               |                   |                        |   |                               |
| Test for overall effect: 2        | Z = 1.27 (        | P = 0.2           | 0)            |                   |                        |   |                               |
| 1.6.2 vs CPAP                     |                   |                   |               |                   |                        |   |                               |
| Göpel 2011                        | 36                | 108               | 82            | 112               | 31.3%                  | 0.46 [0.34, 0.61]                             | <b>.</b>                      |
| Subtotal (95% CI)                 |                   | 108               |               | 112               | 31.3%                  | 0.46 [0.34, 0.61]                             | <b>•</b>                      |
| Total events                      | 36                |                   | 82            |                   |                        |   |                               |
| Heterogeneity: Not app            |                   |                   |               |                   |                        |   |                               |
| Test for overall effect:          | Z = 5.33 (        | P < 0.0           | 0001)         |                   |                        |   |                               |
| 1.6.3 vs MV and surf              |                   |                   |               |                   |                        |   |                               |
| Kribs 2015                        | 80                | 107               | 103           | 104               | 38.4%                  | 0.75 [0.68, 0.84]                             | <u> </u>                      |
| Subtotal (95% CI)                 |                   | 107               |               | 104               | 38.4%                  | 0.75 [0.68, 0.84]                             | <b>♦</b>                      |
| Total events                      | 80                |                   | 103           |                   |                        |   |                               |
| Heterogeneity: Not app            | olicable          |                   |               |                   |                        |   |                               |
| Test for overall effect: 2        | Z = 4.93 (        | P < 0.0           | 0001)         |                   |                        |   |                               |
| Total (95% CI)                    |                   | 315               |               | 316               | 100.0%                 | 0.66 [0.47, 0.93]                             | <b>◆</b>                      |
| Total events                      | 156               |                   | 234           |                   |                        |   |                               |
| Heterogeneity: Tau <sup>2</sup> = | 0.01 0.1 1 10 100 |                   |               |                   |                        |   |                               |
| Test for overall effect: 2        | Z = 2.34 (        | P = 0.0           | 2)            |                   |                        |   | Favours LIST Favours control  |
| Test for subgroup diffe           | rences: C         | hi² = 10          | ).95, df =    | 2 (P =            | 0.004), I <sup>2</sup> | = 81.7%                                       | ravours Lie i ravours control |

Kribs 2015: MV mandatory for control patients. RR 0.61 [0.34, 1.08] if not included

## 1.7 Any MV reported

|  | LIST          |         | Contr         | ol                    |                          | Risk Ratio          | Risk Ratio               |
|--|---------------|---------|---------------|-----------------------|--------------------------|---------------------|--------------------------|
| Study or Subgroup                      | <b>Events</b> | Total   | <b>Events</b> | Total                 | Weight                   | M-H, Random, 95% CI | M-H, Random, 95% CI      |
| 1.7.1 vs InSurE                        |               |         |               |                       |                          |                     |                          |
| Kanmaz 2013                            | 40            | 100     | 49            | 100                   | 22.9%                    | 0.82 [0.60, 1.12]   |                          |
| Mirnia 2013                            | 13            | 66      | 16            | 70                    | 10.4%                    | 0.86 [0.45, 1.65]   | <del></del>              |
| Mohammadizadeh 2015                    | 2             | 19      | 3             | 19                    | 2.1%                     | 0.67 [0.13, 3.55]   |                          |
| Bao 2015                               | 8             | 47      | 10            | 43                    | 7.2%                     | 0.73 [0.32, 1.68]   | <del></del>              |
| Subtotal (95% CI)                      |               | 232     |               | 232                   | 42.6%                    | 0.81 [0.62, 1.05]   | •                        |
| Total events                           | 63            |         | 78            |                       |                          |                     |                          |
| Heterogeneity: Tau <sup>2</sup> = 0.00 | ; $Chi^2 = 0$ | .15, df | = 3 (P = 0)   | 0.99); l <sup>2</sup> | 2 = 0%                   |                     |                          |
| Test for overall effect: Z = 1         | 1.56 (P =     | 0.12)   |               |                       |                          |                     |                          |
| 1.7.2 vs CPAP                          |               |         |               |                       |                          |                     |                          |
| Göpel 2011                             | 36            | 108     | 82            | 112                   | 24.1%                    | 0.46 [0.34, 0.61]   | -                        |
| Subtotal (95% CI)                      |               | 108     |               | 112                   | 24.1%                    | 0.46 [0.34, 0.61]   | <b>•</b>                 |
| Total events                           | 36            |         | 82            |                       |                          |                     |                          |
| Heterogeneity: Not applical            | ble           |         |               |                       |                          |                     |                          |
| Test for overall effect: Z = 5         | 5.33 (P <     | 0.0000  | 1)            |                       |                          |                     |                          |
| 1.7.3 vs MV and surf                   |               |         |               |                       |                          |                     |                          |
| Kribs 2015                             | 80            | 107     | 103           | 104                   | 33.3%                    | 0.75 [0.68, 0.84]   | •                        |
| Subtotal (95% CI)                      |               | 107     |               | 104                   | 33.3%                    | 0.75 [0.68, 0.84]   | <b>♦</b>                 |
| Total events                           | 80            |         | 103           |                       |                          |                     |                          |
| Heterogeneity: Not applical            | ble           |         |               |                       |                          |                     |                          |
| Test for overall effect: Z = 4         |               | 0.0000  | 1)            |                       |                          |                     |                          |
| Total (95% CI)                         |               | 447     |               | 448                   | 100.0%                   | 0.69 [0.53, 0.88]   | <b>•</b>                 |
| Total events                           | 179           |         | 263           |                       |                          |                     | ·                        |
| Heterogeneity: Tau <sup>2</sup> = 0.05 |               | 2.68. d |               | 0.03):                | I <sup>2</sup> = 61%     |                     |                          |
| Test for overall effect: $Z = 2$       |               |         | - (-          | /,                    |                          |                     | 0.01 0.1 1 10            |
| Test for subgroup difference           | `             | ,       | . df = 2 (F   | P = 0.00              | )4), I <sup>2</sup> = 82 | 2.0%                | Favours LIST Favours con |

Kribs 2015: MV mandatory in control patients. RR 0.66 [0.47, 0.94] if not included. Mirnia 2013, Mohammadizadeh 2015 and Bao 2015 reported mechanical ventilation by day 3 of life only.

#### 1.8 Need for extra surfactant dose

|  | LIST          | Γ       | Contr         | ol                    |              | Risk Ratio          | Risk Ratio                               |
|--|---------------|---------|---------------|-----------------------|--------------|---------------------|--|
| Study or Subgroup                      | <b>Events</b> | Total   | <b>Events</b> | Total                 | Weight       | M-H, Random, 95% CI | M-H, Random, 95% CI                      |
| 1.8.1 vs InSurE                        |               |         |               |                       |              |                     |  |
| Kanmaz 2013                            | 22            | 100     | 21            | 100                   | 30.1%        | 1.05 [0.62, 1.78]   | <del>-</del>                             |
| Mirnia 2013                            | 25            | 66      | 22            | 70                    | 39.3%        | 1.21 [0.76, 1.92]   | <del>-</del>                             |
| Mohammadizadeh 2015                    | 9             | 19      | 11            | 19                    | 22.7%        | 0.82 [0.44, 1.51]   | <del></del>                              |
| Bao 2015                               | 8             | 47      | 5             | 43                    | 7.8%         | 1.46 [0.52, 4.13]   | <del>    •  </del>                       |
| Subtotal (95% CI)                      |               | 232     |               | 232                   | 100.0%       | 1.07 [0.80, 1.44]   | •  |
| Total events                           | 64            |         | 59            |                       |              |                     |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00 | ); Chi² = 1   | .38, df | = 3 (P = 0)   | 0.71); ľ              | $^{2} = 0\%$ |                     |  |
| Test for overall effect: Z =           | 0.48 (P =     | 0.63)   |               |                       |              |                     |  |
| Total (95% CI)                         |               | 232     |               | 232                   | 100.0%       | 1.07 [0.80, 1.44]   | •  |
| Total events                           | 64            |         | 59            |                       |              |                     |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00 | ); Chi² = 1   | .38, df | = 3 (P = 0    | ).71); l <sup>2</sup> | 2 = 0%       |                     | 0.01 0.1 1 10                            |
| Test for overall effect: Z =           | 0.48 (P =     | 0.63)   |               |                       |              |                     | 0.01 0.1 1 10 Favours LIST Favours Contr |
| Test for subgroup difference           | ces: Not a    | pplicab | le            |                       |              |                     | 1 avours Lio1 1 avours Conti             |

Göpel 2011 and Kribs 2015 reported the median number of surfactant doses per infant, with no difference.

## 1.9 Pneumothorax

|                                   | LIS1                   | Г        | Contr         | ol       |                  | Risk Ratio          | Risk Ratio                                     |
|-----------------------------------|------------------------|----------|---------------|----------|------------------|---------------------|--|
| Study or Subgroup                 | Events                 | Total    | <b>Events</b> | Total    | Weight           | M-H, Random, 95% CI | M-H, Random, 95% CI                            |
| 1.9.1 vs InSurE                   |                        |          |               |          |                  |                     |  |
| Kanmaz 2013                       | 7                      | 100      | 10            | 100      | 30.3%            | 0.70 [0.28, 1.77]   | <del></del>                                    |
| Mirnia 2013                       | 3                      | 66       | 4             | 70       | 12.2%            | 0.80 [0.18, 3.42]   |  |
| Bao 2015                          | 4                      | 47       | 3             | 43       | 12.5%            | 1.22 [0.29, 5.14]   |  |
| Subtotal (95% CI)                 |                        | 213      |               | 213      | 54.9%            | 0.82 [0.41, 1.62]   |  |
| Total events                      | 14                     |          | 17            |          |                  |                     |  |
| Heterogeneity: Tau <sup>2</sup> = | 0.00; Chi <sup>2</sup> | = 0.41   | , df = 2 (F   | P = 0.82 | $(2); I^2 = 0\%$ |                     |  |
| Test for overall effect:          | Z = 0.58 (             | P = 0.5  | 6)            |          |                  |                     |  |
| 1.9.2 vs CPAP                     |                        |          |               |          |                  |                     |  |
| Göpel 2011                        | 4                      | 108      | 8             | 112      | 18.9%            | 0.52 [0.16, 1.67]   |  |
| Subtotal (95% CI)                 |                        | 108      |               | 112      | 18.9%            | 0.52 [0.16, 1.67]   |  |
| Total events                      | 4                      |          | 8             |          |                  |                     |  |
| Heterogeneity: Not app            | olicable               |          |               |          |                  |                     |  |
| Test for overall effect:          | Z = 1.10 (             | P = 0.2  | 7)            |          |                  |                     |  |
| 1.9.3 vs MV and surf              |                        |          |               |          |                  |                     |  |
| Kribs 2015                        | 5                      | 105      | 13            | 103      | 26.2%            | 0.38 [0.14, 1.02]   | <del></del>                                    |
| Subtotal (95% CI)                 |                        | 105      |               | 103      | 26.2%            | 0.38 [0.14, 1.02]   |  |
| Total events                      | 5                      |          | 13            |          |                  |                     |  |
| Heterogeneity: Not app            | olicable               |          |               |          |                  |                     |  |
| Test for overall effect:          | Z = 1.92 (             | P = 0.0  | 5)            |          |                  |                     |  |
| Total (95% CI)                    |                        | 426      |               | 428      | 100.0%           | 0.61 [0.37, 1.02]   | •  |
| Total events                      | 23                     |          | 38            |          |                  |                     |  |
| Heterogeneity: Tau <sup>2</sup> = | 0.00; Chi <sup>2</sup> | = 2.08   | , df = 4 (F   | P = 0.72 | 2); $I^2 = 0\%$  |                     |  |
| Test for overall effect:          | Z = 1.89 (             | P = 0.0  | 6)            |          | -                |                     | 0.01 0.1 1 10 100 Favours LIST Favours control |
| Test for subgroup diffe           | rences: C              | hi² = 1. | 67, df = 2    | P = 0    | .43), $I^2 = 0$  | 1%                  | 1 avours Elot 1 avours control                 |

## 1.10 PDA

|                                   | LIST                   | -           | Contr                        | ol       |                          | Risk Ratio          | Risk Ratio                    |
|-----------------------------------|------------------------|-------------|------------------------------|----------|--------------------------|---------------------|-------------------------------|
| Study or Subgroup                 | <b>Events</b>          | Total       | <b>Events</b>                | Total    | Weight                   | M-H, Random, 95% CI | M-H, Random, 95% CI           |
| 1.10.1 vs InSurE                  |                        |             |                              |          |                          |                     |                               |
| Kanmaz 2013                       | 28                     | 100         | 32                           | 100      | 10.3%                    | 0.88 [0.57, 1.34]   | -+                            |
| Mirnia 2013                       | 18                     | 66          | 11                           | 70       | 4.2%                     | 1.74 [0.89, 3.39]   | <del>  -</del>                |
| Bao 2015                          | 28                     | 47          | 26                           | 43       | 16.4%                    | 0.99 [0.70, 1.38]   | <del>†</del>                  |
| Subtotal (95% CI)                 |                        | 213         |                              | 213      | 30.9%                    | 1.05 [0.76, 1.44]   | •                             |
| Total events                      | 74                     |             | 69                           |          |                          |                     |                               |
| Heterogeneity: Tau <sup>2</sup> = | 0.03; Chi <sup>2</sup> | = 3.00      | , df = 2 (F                  | P = 0.22 | 2); I <sup>2</sup> = 33% | 0                   |                               |
| Test for overall effect: 2        | Z = 0.28 (             | P = 0.7     | 8)                           |          |                          |                     |                               |
| 1.10.2 vs MV and surf             |                        |             |                              |          |                          |                     |                               |
| Kribs 2015                        | 79                     | 107         | 75                           | 104      | 69.1%                    | 1.02 [0.87, 1.21]   | •                             |
| Subtotal (95% CI)                 |                        | 107         |                              | 104      | 69.1%                    | 1.02 [0.87, 1.21]   | <b>♦</b>                      |
| Total events                      | 79                     |             | 75                           |          |                          |                     |                               |
| Heterogeneity: Not app            | olicable               |             |                              |          |                          |                     |                               |
| Test for overall effect: 2        | Z = 0.28 (             | P = 0.7     | 8)                           |          |                          |                     |                               |
|                                   |                        |             |                              |          |                          |                     |                               |
| Total (95% CI)                    |                        | 320         |                              | 317      | 100.0%                   | 1.02 [0.89, 1.17]   | •                             |
| Total events                      | 153                    |             | 144                          |          |                          |                     |                               |
| Heterogeneity: Tau <sup>2</sup> = | 0.00; Chi <sup>2</sup> | = 2.99      | , df = 3 (F                  | P = 0.39 | 9); $I^2 = 0\%$          |                     | 0.01 0.1 1 10 100             |
| Test for overall effect: 2        | Z = 0.33 (             |             | Favours LIST Favours control |          |                          |                     |                               |
| Test for subgroup diffe           | rences: C              | $hi^2 = 0.$ | 02, df = 1                   | (P = 0)  | .90), $I^2 = 0$          | %                   | . avea.e E.e. Taveare control |

Mirnia 2013: we used data for PDA requiring therapy.

# 1.11 PDA ligation

|                                   | LIS1                   |                 | Contr         | ol              |                       | Risk Ratio                                       | Risk Ratio                   |
|-----------------------------------|------------------------|-----------------|---------------|-----------------|-----------------------|--|------------------------------|
| Study or Subgroup                 | Events                 | Total           | <b>Events</b> | Total           | Weight                | M-H, Random, 95% CI                              | M-H, Random, 95% CI          |
| 1.11.1 vs InSurE                  |                        |                 |               |                 |                       |  |                              |
| Bao 2015<br>Subtotal (95% CI)     | 1                      | 47<br><b>47</b> | 0             | 43<br><b>43</b> | 16.8%<br><b>16.8%</b> | 2.75 [0.12, 65.76]<br><b>2.75 [0.12, 65.76</b> ] |                              |
| Total events                      | 1                      |                 | 0             |                 |                       |  |                              |
| Heterogeneity: Not app            | olicable               |                 |               |                 |                       |  |                              |
| Test for overall effect:          | Z = 0.62 (             | P = 0.5         | 3)            |                 |                       |  |                              |
|                                   |                        |                 |               |                 |                       |  |                              |
| 1.11.2 vs CPAP                    |                        |                 |               |                 |                       |  |                              |
| Göpel 2011                        | 0                      | 108             | 2             | 112             | 18.5%                 | 0.21 [0.01, 4.27]                                |                              |
| Subtotal (95% CI)                 |                        | 108             |               | 112             | 18.5%                 | 0.21 [0.01, 4.27]                                |                              |
| Total events                      | 0                      |                 | 2             |                 |                       |  |                              |
| Heterogeneity: Not app            |                        |                 | 43            |                 |                       |  |                              |
| Test for overall effect:          | Z = 1.02 (             | P = 0.3         | 1)            |                 |                       |  |                              |
| 1.11.3 vs MV and surf             | :                      |                 |               |                 |                       |  |                              |
| Kribs 2015                        | 2                      | 107             | 5             | 104             | 64.7%                 | 0.39 [0.08, 1.96]                                | <del></del>                  |
| Subtotal (95% CI)                 |                        | 107             |               | 104             | 64.7%                 | 0.39 [0.08, 1.96]                                |                              |
| Total events                      | 2                      |                 | 5             |                 |                       |  |                              |
| Heterogeneity: Not app            | olicable               |                 |               |                 |                       |  |                              |
| Test for overall effect:          | Z = 1.14 (             | P = 0.2         | 5)            |                 |                       |  |                              |
| Total (95% CI)                    |                        | 262             |               | 259             | 100.0%                | 0.48 [0.13, 1.77]                                |                              |
| Total events                      | 3                      |                 | 7             |                 |                       |  |                              |
| Heterogeneity: Tau <sup>2</sup> = | 0.00; Chi <sup>2</sup> | = 1.52          | , df = 2 (F   | P = 0.47        | 7); $I^2 = 0\%$       |  | 0.005 0.1 1 10 200           |
| Test for overall effect:          | Z = 1.10 (             | P = 0.2         | 7)            |                 |                       |  | Favours LIST Favours control |
| Test for subgroup diffe           | rences: C              | hi² = 1.        | 52, df = 2    | P = 0           | $.47), I^2 = 0$       | )%   | . avada Eler i avada delitio |

#### 1.12 ROP

|                                     | LIST          | Γ           | Contr         | ol       |                         | Risk Ratio          | Risk Ratio                            |
|-------------------------------------|---------------|-------------|---------------|----------|-------------------------|---------------------|---------------------------------------|
| Study or Subgroup                   | <b>Events</b> | Total       | <b>Events</b> | Total    | Weight                  | M-H, Random, 95% CI | M-H, Random, 95% CI                   |
| 1.12.1 vs InSurE                    |               |             |               |          |                         |                     |                                       |
| Kanmaz 2013                         | 3             | 100         | 4             | 100      | 23.7%                   | 0.75 [0.17, 3.27]   |                                       |
| Mirnia 2013                         | 6             | 66          | 7             | 70       | 44.1%                   | 0.91 [0.32, 2.57]   | <del></del>                           |
| Bao 2015                            | 0             | 47          | 0             | 43       |                         | Not estimable       |                                       |
| Subtotal (95% CI)                   |               | 213         |               | 213      | 67.8%                   | 0.85 [0.37, 1.99]   |                                       |
| Total events                        | 9             |             | 11            |          |                         |                     |                                       |
| Heterogeneity: Tau <sup>2</sup> = 0 |               |             |               | P = 0.83 | 3); $I^2 = 0\%$         |                     |                                       |
| Test for overall effect: 2          | Z = 0.37 (    | P = 0.7     | 1)            |          |                         |                     |                                       |
| 1.12.2 vs CPAP                      |               |             |               |          |                         |                     |                                       |
| Göpel 2011                          | 3             | 108         | 1             | 112      | 10.6%                   | 3.11 [0.33, 29.45]  |                                       |
| Subtotal (95% CI)                   |               | 108         |               | 112      | 10.6%                   | 3.11 [0.33, 29.45]  |                                       |
| Total events                        | 3             |             | 1             |          |                         |                     |                                       |
| Heterogeneity: Not app              | licable       |             |               |          |                         |                     |                                       |
| Test for overall effect: 2          | Z = 0.99 (    | P = 0.3     | 2)            |          |                         |                     |                                       |
| 1.12.3 vs MV and surf               |               |             |               |          |                         |                     |                                       |
| Kribs 2015                          | 2             | 107         | 7             | 104      | 21.6%                   | 0.28 [0.06, 1.31]   | <del></del>                           |
| Subtotal (95% CI)                   |               | 107         |               | 104      | 21.6%                   | 0.28 [0.06, 1.31]   |                                       |
| Total events                        | 2             |             | 7             |          |                         |                     |                                       |
| Heterogeneity: Not app              | licable       |             |               |          |                         |                     |                                       |
| Test for overall effect: 2          | Z = 1.62 (    | P = 0.1     | 0)            |          |                         |                     |                                       |
| Total (95% CI)                      |               | 428         |               | 429      | 100.0%                  | 0.77 [0.36, 1.62]   |                                       |
| Total events                        | 14            |             | 19            |          |                         |                     |                                       |
| Heterogeneity: Tau <sup>2</sup> = 0 | 0.05; Chi²    | = 3.25      | df = 3 (F)    | P = 0.35 | 5); I <sup>2</sup> = 8% |                     | 0.01 0.1 1 10                         |
| Test for overall effect: 2          | Z = 0.70 (    | P = 0.4     | 8)            |          |                         | Fa                  | avours [experimental] Favours [contro |
| Test for subgroup differ            | rences: C     | $hi^2 = 3.$ | 21, df = 2    | P = 0    | .20), $I^2 = 3$         | 37.6%               | avours [experimentar] Tavours [contre |
|                                     |               |             |               |          |                         |                     |                                       |

Kanmaz 2013, Mirnia 2013 and Boa 2015 reported on ROP> grade 2. Göpel 2011 and Kribs 2015 reported on ROP treated by laser or cryotherapy. Mirnia 2013 also reported data for treated ROP (5/66 and 1/70), associated with a total RR of 1.13 [0.31, 4.10]

# 1.13 cPVL

|                                     | LIS1                   | Γ            | Contr         | ol       |                          | Risk Ratio          | Risk Ratio                   |
|-------------------------------------|------------------------|--------------|---------------|----------|--------------------------|---------------------|------------------------------|
| Study or Subgroup                   | Events                 | Total        | <b>Events</b> | Total    | Weight                   | M-H, Random, 95% CI | M-H, Random, 95% CI          |
| 1.13.1 vs InSurE                    |                        |              |               |          |                          |                     |                              |
| Bao 2015                            | 1                      | 47           | 1             | 43       | 18.4%                    | 0.91 [0.06, 14.18]  |                              |
| Subtotal (95% CI)                   |                        | 47           |               | 43       | 18.4%                    | 0.91 [0.06, 14.18]  |                              |
| Total events                        | 1                      |              | 1             |          |                          |                     |                              |
| Heterogeneity: Not app              |                        |              |               |          |                          |                     |                              |
| Test for overall effect: 2          | Z = 0.06 (             | P = 0.9      | 5)            |          |                          |                     |                              |
| 1.13.2 vs CPAP                      |                        |              |               |          |                          |                     |                              |
| Göpel 2011                          | 5                      | 108          | 2             | 112      | 34.9%                    | 2.59 [0.51, 13.08]  |                              |
| Subtotal (95% CI)                   |                        | 108          |               | 112      | 34.9%                    | 2.59 [0.51, 13.08]  |                              |
| Total events                        | 5                      |              | 2             |          |                          |                     |                              |
| Heterogeneity: Not app              |                        |              | >             |          |                          |                     |                              |
| Test for overall effect: 2          | ∠ = 1.15 (             | P = 0.2      | 5)            |          |                          |                     |                              |
| 1.13.3 vs MV and surf               |                        |              |               |          |                          |                     |                              |
| Kribs 2015                          | 4                      | 107          | 11            | 104      | 46.7%                    | 0.35 [0.12, 1.07]   |                              |
| Subtotal (95% CI)                   |                        | 107          |               | 104      | 46.7%                    | 0.35 [0.12, 1.07]   |                              |
| Total events                        | 4                      |              | 11            |          |                          |                     |                              |
| Heterogeneity: Not app              |                        |              |               |          |                          |                     |                              |
| Test for overall effect: 2          | Z = 1.83 (             | P = 0.0      | 7)            |          |                          |                     |                              |
| Total (95% CI)                      |                        | 262          |               | 259      | 100.0%                   | 0.84 [0.21, 3.35]   |                              |
| Total events                        | 10                     |              | 14            |          |                          |                     |                              |
| Heterogeneity: Tau <sup>2</sup> = 0 | 0.74; Chi <sup>2</sup> | = 4.00       | , df = 2 (F   | P = 0.14 | 1); I <sup>2</sup> = 50% | <b>%</b>            | 0.01 0.1 1 10 100            |
| Test for overall effect: 2          | `                      |              | ,             |          |                          |                     | Favours LIST Favours control |
| Test for subgroup differ            | rences: C              | $hi^2 = 4$ . | 00, df = 2    | P = 0    | $.14), I^2 = 5$          | 50.0%               |                              |

## 1.14 Severe IVH

|                                   | LIST                   | Γ             | Contr       | ol       |                          | Risk Ratio          | Risk Ratio                               |
|-----------------------------------|------------------------|---------------|-------------|----------|--------------------------|---------------------|--|
| Study or Subgroup                 | Events                 | Total         | Events      | Total    | Weight                   | M-H, Random, 95% CI | M-H, Random, 95% CI                      |
| 1.14.1 vs InSurE                  |                        |               |             |          |                          |                     |  |
| Kanmaz 2013                       | 10                     | 100           | 16          | 100      | 35.2%                    | 0.63 [0.30, 1.31]   |  |
| Bao 2015                          | 1                      | 47            | 0           | 43       | 2.8%                     | 2.75 [0.12, 65.76]  | -  |
| Subtotal (95% CI)                 |                        | 147           |             | 143      | 37.9%                    | 0.67 [0.33, 1.39]   |  |
| Total events                      | 11                     |               | 16          |          |                          |                     |  |
| Heterogeneity: Tau <sup>2</sup> = |                        |               |             | P = 0.37 | 7); $I^2 = 0\%$          |                     |  |
| Test for overall effect:          | Z = 1.07 (             | P = 0.2       | 8)          |          |                          |                     |  |
| 1.14.2 vs CPAP                    |                        |               |             |          |                          |                     |  |
| Göpel 2011                        | 8                      | 108           | 6           | 112      | 21.7%                    | 1.38 [0.50, 3.85]   | <del>-  </del>                           |
| Subtotal (95% CI)                 |                        | 108           |             | 112      | 21.7%                    | 1.38 [0.50, 3.85]   |  |
| Total events                      | 8                      |               | 6           |          |                          |                     |  |
| Heterogeneity: Not ap             | plicable               |               |             |          |                          |                     |  |
| Test for overall effect:          | Z = 0.62 (             | P = 0.5       | 4)          |          |                          |                     |  |
| 1.14.3 vs MV and sur              | f                      |               |             |          |                          |                     |  |
| Kribs 2015                        | 11                     | 107           | 23          | 104      | 40.4%                    | 0.46 [0.24, 0.90]   |  |
| Subtotal (95% CI)                 | 11                     | 107           | 23          | 104      | 40.4%                    | 0.46 [0.24, 0.90]   |  |
| Total events                      | 11                     |               | 23          |          | 101170                   | 0.10 [0.2., 0.00]   | •  |
| Heterogeneity: Not ap             |                        |               | 20          |          |                          |                     |  |
| Test for overall effect:          | •                      | P = 0.0       | 2)          |          |                          |                     |  |
|                                   | - (                    |               | ,           |          |                          |                     |  |
| Total (95% CI)                    |                        | 362           |             | 359      | 100.0%                   | 0.69 [0.40, 1.17]   | •  |
| Total events                      | 30                     |               | 45          |          |                          |                     |  |
| Heterogeneity: Tau <sup>2</sup> = | 0.07; Chi <sup>2</sup> | $^{2} = 3.87$ | , df = 3 (F | P = 0.28 | 3); I <sup>2</sup> = 22% | 6                   | 0.01 0.1 1 10 100                        |
| Test for overall effect:          | ,                      |               | ,           |          |                          |                     | Favours LIST Favours control             |
| Test for subgroup diffe           | erences: C             | $hi^2 = 3.$   | 07, df = 2  | P = 0    | .22), $I^2 = 3$          | 4.8%                | : 1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1. |

## 1.15 Any IVH reported

|  | LIS1        | -       | Contr       | ol                    |              | Risk Ratio          | Risk Ratio                               |
|--|-------------|---------|-------------|-----------------------|--------------|---------------------|--|
| Study or Subgroup                      | Events      | Total   | Events      | Total                 | Weight       | M-H, Random, 95% CI | M-H, Random, 95% CI                      |
| 1.15.1 vs InSurE                       |             |         |             |                       |              |                     |  |
| Kanmaz 2013                            | 10          | 100     | 16          | 100                   | 24.5%        | 0.63 [0.30, 1.31]   | <del></del>                              |
| Mirnia 2013                            | 13          | 66      | 14          | 70                    | 29.3%        | 0.98 [0.50, 1.94]   | <del></del>                              |
| Mohammadizadeh 2015                    | 1           | 19      | 1           | 19                    | 1.8%         | 1.00 [0.07, 14.85]  |  |
| Bao 2015                               | 1           | 47      | 0           | 43                    | 1.3%         | 2.75 [0.12, 65.76]  | <del>-   -</del>                         |
| Subtotal (95% CI)                      |             | 232     |             | 232                   | 57.0%        | 0.83 [0.51, 1.35]   | •  |
| Total events                           | 25          |         | 31          |                       |              |                     |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00 | 0; Chi² = 1 | .38, df | = 3 (P = 0) | ).71); l <sup>2</sup> | $^{2} = 0\%$ |                     |  |
| Test for overall effect: Z =           | 0.75 (P =   | 0.45)   |             |                       |              |                     |  |
| 1.15.2 vs CPAP                         |             |         |             |                       |              |                     |  |
| Göpel 2011                             | 8           | 108     | 6           | 112                   | 12.8%        | 1.38 [0.50, 3.85]   | <del> </del>                             |
| Subtotal (95% CI)                      |             | 108     |             | 112                   | 12.8%        | 1.38 [0.50, 3.85]   |  |
| Total events                           | 8           |         | 6           |                       |              |                     |  |
| Heterogeneity: Not applica             | able        |         |             |                       |              |                     |  |
| Test for overall effect: Z =           | 0.62 (P =   | 0.54)   |             |                       |              |                     |  |
| 1.15.3 vs MV and surf                  |             |         |             |                       |              |                     |  |
| Kribs 2015                             | 11          | 107     | 23          | 104                   | 30.2%        | 0.46 [0.24, 0.90]   |  |
| Subtotal (95% CI)                      |             | 107     |             | 104                   | 30.2%        | 0.46 [0.24, 0.90]   |  |
| Total events                           | 11          |         | 23          |                       |              |                     |  |
| Heterogeneity: Not applica             | able        |         |             |                       |              |                     |  |
| Test for overall effect: Z =           | 2.25 (P =   | 0.02)   |             |                       |              |                     |  |
| Total (95% CI)                         |             | 447     |             | 448                   | 100.0%       | 0.74 [0.52, 1.07]   | •  |
| Total events                           | 44          |         | 60          |                       |              |                     |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00 | 0; Chi² = 4 | .89, df | = 5 (P = 0  | ).43); l²             | 2 = 0%       |                     |  |
| Test for overall effect: Z =           |             |         | `           | ,.                    |              |                     | 0.01 0.1 1 10 Favours LIST Favours contr |
| Test for subgroup differen             | ,           | ,       | df = 2 (P   | = 0.17)               | $I^2 = 43.1$ | %                   | ravours LIST Favours conti               |

Kanmaz 2013, Bao 2015, Göpel 2015 and Kribs 2015 reported grade 3-4 IVH. Mirnia 2013 reported grade 2-4 IVH. Mohammadizadeh 2015 reported grade 1-4 IVH

## 1.16 NEC (as reported)

|                                   | LIST                   | Г           | Contr         | ol       |                         | Risk Ratio          | Risk Ratio                    |
|-----------------------------------|------------------------|-------------|---------------|----------|-------------------------|---------------------|-------------------------------|
| Study or Subgroup                 | <b>Events</b>          | Total       | <b>Events</b> | Total    | Weight                  | M-H, Random, 95% CI | M-H, Random, 95% CI           |
| 1.16.1 vs InSurE                  |                        |             |               |          |                         |                     |                               |
| Kanmaz 2013                       | 5                      | 100         | 6             | 100      | 17.6%                   | 0.83 [0.26, 2.64]   | <del></del>                   |
| Mirnia 2013                       | 1                      | 66          | 6             | 70       | 5.4%                    | 0.18 [0.02, 1.43]   |                               |
| Subtotal (95% CI)                 |                        | 166         |               | 170      | 23.0%                   | 0.49 [0.11, 2.13]   |                               |
| Total events                      | 6                      |             | 12            |          |                         |                     |                               |
| Heterogeneity: Tau <sup>2</sup> = |                        |             |               | P = 0.19 | $(9); I^2 = 419$        | %                   |                               |
| Test for overall effect:          | Z = 0.95 (             | P = 0.3     | 4)            |          |                         |                     |                               |
| 1.16.2 vs CPAP                    |                        |             |               |          |                         |                     |                               |
| Göpel 2011                        | 3                      | 108         | 4             | 112      | 10.8%                   | 0.78 [0.18, 3.39]   | <del></del>                   |
| Subtotal (95% CI)                 |                        | 108         |               | 112      | 10.8%                   | 0.78 [0.18, 3.39]   |                               |
| Total events                      | 3                      |             | 4             |          |                         |                     |                               |
| Heterogeneity: Not app            | olicable               |             |               |          |                         |                     |                               |
| Test for overall effect:          | Z = 0.33 (             | P = 0.7     | 4)            |          |                         |                     |                               |
| 1.16.3 vs MV and surf             | F                      |             |               |          |                         |                     |                               |
| Kribs 2015                        | 19                     | 107         | 17            | 104      | 66.1%                   | 1.09 [0.60, 1.97]   | -                             |
| Subtotal (95% CI)                 |                        | 107         |               | 104      | 66.1%                   | 1.09 [0.60, 1.97]   | •                             |
| Total events                      | 19                     |             | 17            |          |                         |                     |                               |
| Heterogeneity: Not app            | olicable               |             |               |          |                         |                     |                               |
| Test for overall effect:          | Z = 0.27 (             | P = 0.7     | 9)            |          |                         |                     |                               |
| Total (95% CI)                    |                        | 381         |               | 386      | 100.0%                  | 0.91 [0.56, 1.47]   | •                             |
| Total events                      | 28                     |             | 33            |          |                         |                     |                               |
| Heterogeneity: Tau <sup>2</sup> = | 0.00; Chi <sup>2</sup> | = 2.85      | , df = 3 (F   | P = 0.41 | 1); I <sup>2</sup> = 0% |                     | 0.01 0.1 1 10 100             |
| Test for overall effect:          | Z = 0.40 (             | P = 0.6     | 9)            |          |                         |                     | Favours LIST Favours control  |
| Test for subgroup diffe           | rences: C              | $hi^2 = 1.$ | 04, df = 2    | P = 0    | .59), $I^2 = 0$         | )%                  | Tavodio EloT Tavodio Collifor |

Göpel 2015 and Kribs 2015 reported a combined outcome of NEC or focal intestinal perforation requiring surgery.
Kanmaz 2013 and Mirnia 2013 reported NEC Bell stages 2 and 3.

## 1.17 Death or severe morbidity

|                                   | LIST                   |                   | Contr         | ol                |                         | Risk Ratio   | Risk Ratio                     |
|-----------------------------------|------------------------|-------------------|---------------|-------------------|-------------------------|--|--------------------------------|
| Study or Subgroup                 | <b>Events</b>          | Total             | <b>Events</b> | Total             | Weight                  | M-H, Random, 95% CI                                    | M-H, Random, 95% CI            |
| 1.17.1 vs CPAP                    |                        |                   |               |                   |                         |  |                                |
| Göpel 2011<br>Subtotal (95% CI)   | 16                     | 108<br><b>108</b> | 16            | 112<br><b>112</b> | 12.2%<br><b>12.2%</b>   | 1.04 [0.55, 1.97]<br><b>1.04 [0.55, 1.97]</b>          | •                              |
| Total events                      | 16                     |                   | 16            |                   |                         |  |                                |
| Heterogeneity: Not app            | olicable               |                   |               |                   |                         |  |                                |
| Test for overall effect:          | Z = 0.11 (             | P = 0.9           | 1)            |                   |                         |  |                                |
| 1.17.2 vs MV and surf             |                        |                   |               |                   |                         |  |                                |
| Kribs 2015<br>Subtotal (95% CI)   | 53                     | 107<br><b>107</b> | 67            | 104<br><b>104</b> | 87.8%<br><b>87.8%</b>   | 0.77 [0.61, 0.98]<br><b>0.77 [0.61</b> , <b>0.98</b> ] | <b>♦</b>                       |
| Total events                      | 53                     |                   | 67            |                   |                         |  |                                |
| Heterogeneity: Not app            | olicable               |                   |               |                   |                         |  |                                |
| Test for overall effect:          | Z = 2.16 (             | P = 0.0           | 3)            |                   |                         |  |                                |
| Total (95% CI)                    |                        | 215               |               | 216               | 100.0%                  | 0.80 [0.64, 1.00]                                      | <b>•</b>                       |
| Total events                      | 69                     |                   | 83            |                   |                         |  |                                |
| Heterogeneity: Tau <sup>2</sup> = | 0.00; Chi <sup>2</sup> | = 0.79            | , df = 1 (F   | P = 0.37          | 7); I <sup>2</sup> = 0% |  | 0.01 0.1 1 10 100              |
| Test for overall effect: 2        | Z = 1.98 (             | P = 0.0           | 5)            |                   |                         |  | Favours LIST Favours control   |
| Test for subgroup diffe           | rences: C              | $hi^2 = 0.$       | 74, df = 1    | (P = 0)           | .39), $I^2 = 0$         | 0%   | 1 avours Lio1 1 avours control |

Both studies reported a combined ouctome of death, BDP, severe IVH, PVL, or surgery for NEC, FIP or ROP.
Kribs 2015 also include BPD

# 1.18 Failed first attempt

|  | LIST                    | Γ        | Contr         | ol                    |                    | Risk Ratio          | Risk Ratio                    |
|--|-------------------------|----------|---------------|-----------------------|--------------------|---------------------|-------------------------------|
| Study or Subgroup                                  | <b>Events</b>           | Total    | <b>Events</b> | Total                 | Weight             | M-H, Random, 95% CI | M-H, Random, 95% CI           |
| 1.18.1 vs InSurE                                   |                         |          |               |                       |                    |                     |                               |
| Kanmaz 2013  | 18                      | 100      | 10            | 100                   | 27.2%              | 1.80 [0.87, 3.70]   | <del> </del>                  |
| Mohammadizadeh 2015                                | 4                       | 35       | 10            | 36                    | 16.9%              | 0.41 [0.14, 1.19]   | <del></del>                   |
| Bao 2015   | 5                       | 47       | 6             | 43                    | 15.9%              | 0.76 [0.25, 2.32]   | -                             |
| Subtotal (95% CI)                                  |                         | 182      |               | 179                   | 60.0%              | 0.89 [0.36, 2.21]   |                               |
| Total events                                       | 27                      |          | 26            |                       |                    |                     |                               |
| Heterogeneity: Tau <sup>2</sup> = 0.4 <sup>2</sup> | 1; Chi <sup>2</sup> = 5 | 5.45, df | = 2 (P = 0    | 0.07); I <sup>2</sup> | 2 = 63%            |                     |                               |
| Test for overall effect: Z =                       | 0.26 (P =               | 0.80)    |               |                       |                    |                     |                               |
|  |                         |          |               |                       |                    |                     |                               |
| 1.18.2 vs MV and surf                              |                         |          |               |                       |                    |                     |                               |
| Kribs 2015   | 29                      | 107      | 28            | 112                   | 40.0%              | 1.08 [0.69, 1.69]   | <del>*</del>                  |
| Subtotal (95% CI)                                  |                         | 107      |               | 112                   | 40.0%              | 1.08 [0.69, 1.69]   | •                             |
| Total events                                       | 29                      |          | 28            |                       |                    |                     |                               |
| Heterogeneity: Not applica                         | able                    |          |               |                       |                    |                     |                               |
| Test for overall effect: Z =                       | 0.35 (P =               | 0.72)    |               |                       |                    |                     |                               |
|  |                         |          |               |                       |                    |                     |                               |
| Total (95% CI)                                     |                         | 289      |               | 291                   | 100.0%             | 1.00 [0.59, 1.68]   | •                             |
| Total events                                       | 56                      |          | 54            |                       |                    |                     |                               |
| Heterogeneity: Tau <sup>2</sup> = 0.13             | $3; Chi^2 = 5$          | 5.47, df | = 3 (P = 0)   | 0.14); ľ              | <sup>2</sup> = 45% |                     | 0.01 0.1 1 10                 |
| Test for overall effect: Z =                       | 0.00 (P =               | 1.00)    |               |                       |                    |                     | Favours LIST Favours control  |
| Test for subgroup differen                         | ces: Chi²               | = 0.15,  | df = 1 (P     | = 0.70)               | $I^2 = 0\%$        |                     | 1 avours EloT T avours contin |

# 1.19 Desaturation during procedure

|   | LIST          |                   | Contr         | ol                |                       | Risk Ratio                                     | Risk Ratio                                    |
|---|---------------|-------------------|---------------|-------------------|-----------------------|--|---|
| Study or Subgroup   | <b>Events</b> | Total             | <b>Events</b> | Total             | Weight                | M-H, Random, 95% CI                            | M-H, Random, 95% CI                           |
| 1.19.1 vs InSurE  |               |                   |               |                   |                       |  |   |
| Kanmaz 2013   | 18            | 100               | 17            | 100               | 28.2%                 | 1.06 [0.58, 1.93]                              | -   |
| Mirnia 2013   | 3             | 66                | 15            | 70                | 21.1%                 | 0.21 [0.06, 0.70]                              | <del></del>                                   |
| Mohammadizadeh 2015<br>Subtotal (95% CI)  | 3             | 35<br><b>201</b>  | 7             | 36<br><b>206</b>  | 20.2%<br><b>69.6%</b> | 0.44 [0.12, 1.57]<br><b>0.51 [0.18, 1.44</b> ] |   |
| Total events  | 24            |                   | 39            |                   |                       |  |   |
| Heterogeneity: Tau <sup>2</sup> = 0.57<br>Test for overall effect: Z = 1.19.2 vs MV and surf        |               |                   | = 2 (P = (    | 0.04); l²         | 2 = 69%               |  |   |
| Kribs 2015<br>Subtotal (95% CI)   | 60            | 107<br><b>107</b> | 27            | 104<br><b>104</b> | 30.4%<br><b>30.4%</b> | 2.16 [1.50, 3.11]<br><b>2.16 [1.50, 3.11]</b>  | •   |
| Total events Heterogeneity: Not applica Test for overall effect: Z = 4                              |               | 0.0001            | 27            |                   |                       |  |   |
| Total (95% CI)  |               | 308               |               | 310               | 100.0%                | 0.78 [0.30, 2.02]                              |   |
| Total events Heterogeneity: Tau² = 0.73 Test for overall effect: Z = 0 Test for subgroup difference | 0.50 (P =     | 0.61)             | •             |                   |                       |  | 0.01 0.1 1 10<br>Favours LIST Favours control |

## 1.20 Cough during procedure

|  | LIST           | Г       | Contr         | ol                    |                    | Risk Ratio           | Risk Ratio                   |
|--|----------------|---------|---------------|-----------------------|--------------------|----------------------|------------------------------|
| Study or Subgroup                      | <b>Events</b>  | Total   | <b>Events</b> | Total                 | Weight             | M-H, Random, 95% CI  | M-H, Random, 95% CI          |
| 1.20.1 vs InSure                       |                |         |               |                       |                    |                      |                              |
| Mirnia 2013                            | 8              | 66      | 0             | 70                    | 43.6%              | 18.01 [1.06, 306.05] | -                            |
| Mohammadizadeh 2015                    | 3              | 35      | 4             | 36                    | 56.4%              | 0.77 [0.19, 3.20]    | <del></del>                  |
| Subtotal (95% CI)                      |                | 101     |               | 106                   | 100.0%             | 3.05 [0.10, 90.71]   |                              |
| Total events                           | 11             |         | 4             |                       |                    |                      |                              |
| Heterogeneity: Tau <sup>2</sup> = 4.79 | 9; $Chi^2 = 4$ | .66, df | = 1 (P = 0)   | 0.03); I <sup>2</sup> | <sup>2</sup> = 79% |                      |                              |
| Test for overall effect: Z =           | 0.64 (P =      | 0.52)   |               |                       |                    |                      |                              |
|  |                |         |               |                       |                    |                      |                              |
|  |                |         |               |                       |                    |                      | 0.01 0.1 1 10                |
|  |                |         |               |                       |                    |                      | Favours LIST Favours control |

## 1.21 Surfactant reflux during procedure

|                          | LIST         | -        | Contr         | ol       |             | Risk Ratio          | Risk Ratio                        |
|--------------------------|--------------|----------|---------------|----------|-------------|---------------------|-----------------------------------|
| Study or Subgroup        | Events       | Total    | <b>Events</b> | Total    | Weight      | M-H, Random, 95% CI | M-H, Random, 95% CI               |
| 1.21.1 vs InSurE         |              |          |               |          |             |                     |                                   |
| Kanmaz 2013              | 21           | 100      | 10            | 100      | 58.8%       | 2.10 [1.04, 4.23]   | <del></del>                       |
| Mirnia 2013              | 4            | 66       | 1             | 70       | 6.2%        | 4.24 [0.49, 36.98]  | <del>-   -</del>                  |
| Bao 2015                 | 17           | 47       | 5             | 43       | 35.0%       | 3.11 [1.26, 7.71]   |                                   |
| Subtotal (95% CI)        |              | 213      |               | 213      | 100.0%      | 2.52 [1.47, 4.31]   |                                   |
| Total events             | 42           |          | 16            |          |             |                     |                                   |
| Heterogeneity: Tau² =    | : 0.00; Chi² | = 0.69   | , df = 2 (F   | P = 0.7' | 1); I² = 0% |                     |                                   |
| Test for overall effect: | Z = 3.37 (   | P = 0.0  | (800          |          |             |                     |                                   |
|                          |              |          |               |          |             |                     |                                   |
|                          |              |          |               |          |             |                     | 0.01 0.1 1 10                     |
| Toot for aubaroup diffe  | oronooo, N   | ot oppli | iooblo        |          |             | Fa                  | avours [experimental] Favours [co |

Test for subgroup differences: Not applicable