**Additional file 1. Supplementary Tables**

**Table S1.** Overview of published methodological and tutorial articles on missing *binary* outcome data in systematic reviews

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Article** | **MOD methods** | **MOD assumption** | **Missingness parameter** | **Missingness parameter structure** | **Analysis framework** | **MA model** | **MA parameters** | **Other** |
| *Pairwise meta-analysis* |
| [1] | Direct imputation | MAR, BC, WC, UI | – | – | Frequentist | FE | MA OR | With and without accountability of MOD uncertainty |
| [2] | Direct imputation, two-stage pattern-mixture model | MAR, UI, AME, AMNE, BC, WC, pC, pE, p | IMOR\* | identical intervention-specific | Frequentist | FE and RE1 | MA RR, $I^{2}$ | Various weighting schemes for MOD uncertainty |
| [3] | Two-stage pattern-mixture model | MAR, AME, AMNE, BC, WC | IMOR\* | identical trial-specific, unconditional, correlated  | TS, GH | FE and RE | MA OR, $τ^{2}$ |  –  |
| [4] | Two-stage pattern-mixture model, One-stage selection model | MAR, UI, BC, WC | IMOR\* | identical common, identical intervention-specific, identical trial-specific, independent unconditional  | Bayesian | FE and RE | MA OR | Different variances for the log IMOR |
| [5] | Direct imputation | MAR, AMNE, AME, BC, WC, pC, p | RI\* | identical intervention-specific  | Frequentist | FE | MA OR, MA RR | Different values for RI, no accountability of MOD uncertainty |
| [6]2 | Direct imputation, two-stage pattern-mixture model | MAR, UI, BC, WC, LOCF | IMOR\* | identical intervention-specific  | Frequentist | RE | MA OR | With and without accountability of MOD uncertainty |
| [7] | Two-stage pattern-mixture model | MAR, LOCF | Sensitivity and specificity | identical intervention-specific | Bayesian | RE | MA OR, $τ^{2}$ | Different priors on diagnostic parameters |
| [8] | One-stage pattern-mixture model, direct imputation | MAR, AMNE3, BC3, WC3 | $p^{m}$, IMOR\* | independent common  | Bayesian | FE and RE | MA OR, $τ^{2}$ | Different priors on $p^{m}$, model fit ($\overbar{D}\_{res}$) |
| *Network meta-analysis* |
| [9] | One-stage selection model | MAR, AME, AMNE, BC, WC | IMOR\* | identical intervention-specific  | Bayesian | RE | NMA OR, $τ^{2}$, SUCRA | With and without accountability of MOD uncertainty  |

AME, more missing cases are events in both arms; AMNE, all missing cases are non-events in both arms; BC, best-case scenario for the experimental arm; $\overbar{D}\_{res}$, posterior mean of residual deviance; FE, fixed-effect model; GH, Gauss–Hermite approximation; IMOR, informative missingness odds ratio; LOCF, last-observation carried forward; MA, meta-analysis; MAR, missing at random; MOD, missing outcome data; p, arm-specific observed risk; pC, control-specific observed risk; pE, experimental-specific observed risk; $p^{m}$, probability of event among missing participants; RE, random-effects model; RI, relative incidence among those with missing data compared to those with available data in the same arm; SUCRA, surface under the cumulative ranking curve; TS, Taylor series approximation; UI, uncertainty interval by Gamble and Hollis; WC, worst-case scenario for the experimental arm.

1Results are not shown in the publication.

2A review and tutorial on proposed methods to handle missing binary outcome data in pairwise meta-analysis.

3For each assumption, missing outcome data were imputed before meta-analysis and results were compared with those after considering specific missingness parameter(s).

\*The respective scenarios imply that it is more or less like that missing cases will have the event in all interventions or the experimental or the control alone.

**References**

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| **Prevalence and balance of missing outcome data in each network** |

**Table S2. Distribution of total percentage of missing outcome data per network**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **ID** | **minimum** | **1st quartile** | **median** | **mean** | **3rd quartile** | **maximum** | **prevalence†** |
| 1 | 0.00% | 1.47% | 3.63% | 5.46% | 6.94% | 24.14% | Low |
| 2 | 0.49% | 1.34% | 2.15% | 3.33% | 3.06% | 19.00% | Low |
| 3 | 1.44% | 10.17% | 12.91% | 15.24% | 19.10% | 34.72% | Moderate |
| 4 | 1.97% | 2.54% | 4.07% | 4.27% | 6.01% | 6.81% | Low |
| 5 | 1.35% | 3.42% | 4.83% | 4.65% | 5.31% | 8.02% | Low |
| 6 | 1.13% | 1.38% | 2.74% | 4.20% | 6.24% | 10.74% | Low |
| 7 | 0.00% | 7.68% | 13.79% | 13.52% | 17.80% | 42.80% | Moderate |
| 8 | 0.69% | 1.38% | 1.68% | 1.99% | 2.91% | 3.30% | Low |
| 9 | 4.73% | 6.25% | 7.71% | 8.06% | 8.95% | 14.11% | Moderate |
| 10 | 8.99% | 26.75% | 29.07% | 30.98% | 39.78% | 49.66% | Large |
| 11 | 0.00% | 4.46% | 7.46% | 7.71% | 11.02% | 20.00% | Moderate |
| 12 | 0.00% | 13.62% | 18.44% | 17.31% | 22.55% | 29.11% | Moderate |
| 13 | 4.18% | 9.65% | 11.87% | 12.43% | 16.00% | 19.90% | Moderate |
| 14 | 0.00% | 12.07% | 15.65% | 18.45% | 23.81% | 42.55% | Moderate |
| 15 | 0.00% | 0.32% | 8.69% | 9.01% | 17.39% | 18.68% | Moderate |
| 16 | 3.65% | 4.35% | 5.28% | 5.28% | 6.22% | 6.92% | Moderate |
| 17 | 2.10% | 12.57% | 19.28% | 17.85% | 22.64% | 38.23% | Moderate |
| 18 | 0.00% | 12.79% | 17.68% | 17.73% | 23.20% | 38.71% | Moderate |
| 19 | 4.49% | 12.45% | 16.81% | 16.54% | 22.12% | 28.47% | Moderate |
| 20 | 1.89% | 4.41% | 5.22% | 6.07% | 6.07% | 17.46% | Moderate |
| 21 | 1.73% | 1.85% | 4.70% | 4.38% | 6.76% | 6.87% | Low |
| 22 | 3.31% | 8.40% | 14.45% | 18.80% | 24.84% | 57.83% | Moderate |
| 23 | 0.15% | 0.38% | 0.57% | 0.61% | 0.88% | 1.06% | Low |
| 24 | 0.00% | 0.00% | 4.54% | 11.54% | 13.23% | 53.16% | Low |
| 25 | 0.00% | 3.19% | 9.27% | 10.63% | 14.38% | 42.43% | Moderate |
| 26 | 0.00% | 0.00% | 1.43% | 2.13% | 1.64% | 7.56% | Low |
| 27 | 0.00% | 6.89% | 11.08% | 12.54% | 18.12% | 29.77% | Moderate |
| 28 | 0.61% | 1.93% | 3.89% | 5.57% | 7.96% | 19.47% | Low |
| 29 | 0.00% | 0.00% | 0.00% | 2.15% | 0.18% | 14.71% | Low |

**†**Missingness was considered to be low for median up to 5% (low attrition bias risk), large for median above 20% (large attrition bias risk) and moderate otherwise (moderate attrition bias).

**Table S3. Distribution of the difference in %MOD between compared arms per network**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **ID** | **minimum** | **1st quartile** | **median** | **mean** | **3rd quartile** | **maximum** | **balance†** |
| 1 | 0.00% | 0.63% | 1.89% | 3.07% | 4.29% | 20.88% | Yes  |
| 2 | 0.09% | 0.57% | 1.79% | 2.14% | 2.55% | 11.03% | Yes |
| 3 | 0.02% | 4.02% | 5.43% | 6.67% | 8.76% | 15.54% | Yes |
| 4 | 0.65% | 1.21% | 1.95% | 1.69% | 2.21% | 2.32% | Yes |
| 5 | 0.43% | 2.07% | 3.68% | 4.44% | 7.35% | 9.89% | Yes  |
| 6 | 0.82% | 1.48% | 3.73% | 4.32% | 7.61% | 8.06% | Yes |
| 7 | 0.00% | 3.67% | 5.62% | 6.96% | 8.79% | 19.28% | Yes |
| 8 | 0.41% | 0.87% | 1.47% | 1.89% | 2.93% | 3.90% | Yes |
| 9 | 0.56% | 1.65% | 3.44% | 4.15% | 4.87% | 10.98% | Yes |
| 10 | 6.81% | 17.11% | 20.58% | 24.93% | 25.85% | 57.35% | No |
| 11 | 0.00% | 0.20% | 2.40% | 4.50% | 4.79% | 23.81% | Yes |
| 12 | 0.00% | 2.47% | 6.38% | 8.08% | 13.84% | 20.15% | Yes |
| 13 | 1.45% | 6.27% | 10.37% | 10.14% | 12.51% | 19.61% | No |
| 14 | 0.00% | 1.53% | 4.44% | 6.94% | 11.41% | 17.56% | Yes |
| 15 | 0.00% | 0.47% | 2.21% | 2.06% | 3.80% | 3.83% | Yes |
| 16 | 0.02% | 0.48% | 0.78% | 0.77% | 1.06% | 1.51% | Yes |
| 17 | 0.00% | 2.57% | 6.66% | 8.05% | 9.93% | 23.82% | No |
| 18 | 0.00% | 3.05% | 5.86% | 7.91% | 7.60% | 46.11% | Yes |
| 19 | 0.12% | 1.96% | 4.84% | 5.24% | 7.32% | 12.72% | Yes |
| 20 | 0.00% | 1.53% | 3.18% | 4.02% | 6.80% | 9.52% | Yes |
| 21 | 0.11% | 1.28% | 2.48% | 2.61% | 4.50% | 4.67% | Yes |
| 22 | 0.82% | 3.59% | 5.00% | 6.32% | 8.24% | 15.92% | Yes |
| 23 | 0.00% | 0.07% | 0.11% | 0.18% | 0.32% | 0.39% | Yes  |
| 24 | 0.00% | 0.00% | 2.91% | 3.78% | 7.82% | 9.94% | Yes |
| 25 | 0.00% | 1.68% | 3.99% | 5.84% | 8.45% | 26.18% | Yes |
| 26 | 0.00% | 0.00% | 0.08% | 0.25% | 0.51% | 0.68% | Yes |
| 27 | 0.00% | 0.48% | 2.51% | 4.66% | 7.53% | 23.05% | Yes  |
| 28 | 0.00% | 0.85% | 1.10% | 1.61% | 1.81% | 5.79% | Yes  |
| 29 | 0.00% | 0.00% | 0.00% | 0.14% | 0.00% | 0.97% | Yes  |

**†**Networks with median larger than 6.5% were considered to have imbalance in MOD between the compared intervention arms.

MOD: missing outcome data

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| **Agreement between on average missing at random and extreme scenarios** |

**Table S4. Agreement on direction, strength of evidence and extent of heterogeneity**

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| --- |
| **Basic parameters (log odds ratio)** |
|  | MME | MMNE | BC  | WC  |
| *Strength of evidence*1 |
| MAR | Weak | Strong | Weak | Strong | Weak | Strong | Weak | Strong |
| Weak  | 60% | 1% | 60% | 1% | 53% | 8% | 60% | 1% |
| Strong | 1% | 38% | 1% | 38% | 1% | 39% | 4% | 35% |
| Kappa | 0.98 (0.95, 1.00)\* | 0.98 (0.95, 1.00)\* | 0.83 (0.75, 0.91)† | 0.89 (0.83, 0.96)\* |
| *Direction of evidence*2 |
| MAR | First | Second | First | Second | First | Second | First | Second |
| First | 85% | 0% | 85% | 0% | 85% | 0% | 80% | 5% |
| Second | 1% | 14% | 0% | 15% | 2% | 12% | 0% | 15% |
| Kappa | 0.95 (0.89, 1.00)\* | 0.98 (0.94, 1.00)\* | 0.91 (0.82, 1.00)\* | 0.81 (0.70, 0.92)† |
| *Extent of between-trial variance*3 |
| MAR | LO | MO | LA | LO | MO | LA | LO | MO | LA | LO | MO | LA |
| Low | 62% | 7% | 0% | 69% | 0% | 0% | 62% | 7% | 0% | 69% | 0% | 0% |
| Moderate | 0% | 10% | 0% | 0% | 10% | 0% | 0% | 10% | 0% | 3% | 7% | 0% |
| Large | 0% | 7% | 14% | 0% | 0% | 21% | 0% | 7% | 14% | 0% | 0% | 21% |
| Kappa | 0.73 (0.49, 0.98)† | 1.00  | 0.73 (0.49, 0.98)† | 0.92 (0.78, 1.00)† |
| **Inconsistency factor (log odds ratio)** |
|  | MME | MMNE | BC  | WC  |
| *Strength of evidence*1 |
| MAR | Weak | Strong | Weak | Strong | Weak | Strong | Weak | Strong |
| Weak | 94% | 0% | 94% | 0% | 94% | 0% | 94% | 0% |
| Strong | 0% | 6% | 0% | 6% | 0% | 6% | 1% | 5% |
| Kappa | 1.00 | 1.00 | 1.00 | 1.00 |
| *Direction of evidence*2 |
| MAR | Positive  | Negative | Positive  | Negative | Positive  | Negative | Positive  | Negative |
| Positive | 46% | 0% | 46% | 0% | 46% | 0% | 46% | 0% |
| Negative | 1% | 53% | 1% | 53% | 1% | 53% | 1% | 53% |
| Kappa | 0.98 (0.96, 1.00)\* | 0.97 (0.93, 1.00)\* | 0.96 (0.91, 1.00)\* | 0.98 (0.96, 1.00)\* |

BC: best-case scenario; LA: large; LO: low; MAR: (on average) missing at random; MME: more missing cases are events in all interventions; MMNE: more missing cases are non-events in all interventions; MO: moderate; WC: worst-case scenario.

1Strong evidence when 0 (in the log scale) is not included in the 95% credible interval, otherwise weak evidence.

2Whether the estimated log odds ratio favors the first or second intervention in a comparison. In case of inconsistency factor, whether the difference between direct and indirect estimate for a specific comparison is positive or negative.

3Estimated between-trial variance is low, moderate and large when it is smaller than the median, between the median and 3rd quartile and larger than the 3rd quartile, respectively, of the selected empirical distribution for the true between-trial variance.

\*Almost perfect agreement (0.81 – 1.00);

†95% confidence interval is too wide to judge the level of agreement with confidence.

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| **Agreement between accounting and discounting uncertainty due to missingness** |

**Table S5. Agreement on direction, strength of evidence and extent of heterogeneity**

|  |
| --- |
| **Basic parameters (log odds ratio)** |
|  | MAR w/o | MME w/o | MMNE w/o | BC w/o | WC w/o |
| *Strength of evidence*1 |
| With  | Weak | Strong | Weak | Strong | Weak | Strong | Weak | Strong | Weak | Strong |
| Weak  | 56% | 5% | 57% | 4% | 57% | 4% | 49% | 5% | 61% | 3% |
| Strong | 0% | 39% | 0% | 39% | 0% | 39% | 0% | 46% | 0% | 35% |
| Kappa | 0.90 (0.84, 0.96)\* | 0.92 (0.86, 0.98)\* | 0.92 (0.86, 0.98)\* | 0.90 (0.84, 0.96)\* | 0.93 (0.87, 0.98)\* |
| *Direction of evidence*2 |
| With | First | Second | First | Second | First | Second | First | Second | First | Second |
| First | 85% | 0% | 86% | 0% | 85% | 0% | 88% | 0% | 76% | 4% |
| Second | 1% | 14% | 0% | 14% | 0% | 15% | 1% | 11% | 0% | 20% |
| Kappa | 0.95 (0.89, 1.00)\* | 1.00 | 0.98 (0.94, 1.00)\* | 0.95 (0.88, 1.00)\* | 0.89 (0.81, 0.97)\* |
| *Extent of between-trial variance*3 |
| With | LO | MO | LA | LO | MO | LA | LO | MO | LA | LO | MO | LA | LO | MO | LA |
| Low | 59% | 10% | 0% | 62% | 0% | 0% | 59% | 10% | 0% | 62% | 0% | 0% | 69% | 3% | 0% |
| Moderate | 0% | 10% | 0% | 0% | 24% | 0% | 0% | 10% | 0% | 0% | 24% | 0% | 0% | 7% | 0% |
| Large | 0% | 0% | 21% | 0% | 0% | 14% | 0% | 0% | 21% | 0% | 0% | 14% | 0% | 0% | 21% |
| Kappa | 0.80 (0.60, 1.00)† | 1.00 | 0.80 (0.60, 1.00)† | 1.00 | 0.92 (0.78, 1.00)† |
| **Inconsistency factor (log odd ratio)** |
|  | MAR w/o | MME w/o | MMNE w/o | BC w/o | WC w/o |
| *Strength of evidence*1 |
| With | Weak | Strong | Weak | Strong | Weak | Strong | Weak | Strong | Weak | Strong |
| Weak | 94% | 0% | 94% | 0% | 94% | 0% | 94% | 0% | 95% | 0% |
| Strong | 0% | 6% | 0% | 6% | 0% | 6% | 1% | 5% | 0% | 5% |
| Kappa | 1.00 | 1.00 | 1.00 | 0.93 (0.79, 1.00)\* | 1.00 |
| *Direction of evidence*2 |
| With | Positive  | Negative | Positive  | Negative | Positive  | Negative | Positive  | Negative | Positive  | Negative |
| Positive | 64% | 0% | 46% | 1% | 47% | 1% | 46% | 1% | 46% | 1% |
| Negative | 1% | 52% | 1% | 51% | 1% | 51% | 1% | 51% | 1% | 51% |
| Kappa | 0.97 (0.93, 1.00)\* | 0.96 (0.91, 1.00)\* | 0.97 (0.93, 1.00)\* | 0.96 (0.91, 1.00)\* | 0.96 (0.91, 1.00)\* |

BC: best-case scenario; LA: large; LO: low; MAR: missing at random; MME: more missing cases are event in all interventions; MMNE: more missing cases are non-events in all interventions; MO: moderate; WC: worst-case scenario; w/o: without.

1Strong evidence when 0 (in the log scale) is not included in the 95% credible interval, otherwise weak evidence.

2Whether the estimated log odds ratio favors the first or second intervention in the respective basic parameter. In case of inconsistency factor, whether the difference between direct and indirect estimate for a specific comparison is positive or negative.

3Estimated between-trial variance is low, moderate and large when it is smaller than the median, between the median and 3rd quartile or larger than the 3rd quartile, respectively, of the selected empirical distribution for the true between-trial variance.

\*Almost perfect agreement (0.81 – 1.00); †95% confidence interval is too wide to judge the level of agreement with confidence.

|  |
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| **Agreement between identical and hierarchical structure of log IMOR** |

**Table S6. Agreement on direction, strength of evidence and extent of heterogeneity**

|  |
| --- |
| **Basic parameters (log odds ratio)** |
|  | Common-within-network | Trial-specific | Intervention-specific |
| *Strength of evidence*1 |
| IDE | Weak | Strong | Weak | Strong | Weak | Strong |
| Weak  | 57% | 1% | 56% | 0% | 60% | 1% |
| Strong | 2% | 41% | 2% | 42% | 1% | 38% |
| Kappa | 0.95 (0.91, 1.00)\* | 0.95 (0.91, 1.00)\* | 0.96 (0.93, 1.00)\* |
| *Direction of evidence*2 |
| IDE | First | Second | First | Second | First | Second |
| First | 86% | 0% | 86% | 0% | 85% | 1% |
| Second | 0% | 14% | 0% | 14% | 0% | 14% |
| Kappa | 1.00 | 1.00 | 0.98 (0.93, 1.00)\* |
| *Extent of between-trial variance*3 |
| IDE | LO | MO | LA | LO | MO | LA | LO | MO | LA |
| Low | 62% | 0% | 0% | 62% | 0% | 0% | 66% | 0% | 0% |
| Moderate | 10% | 7% | 0% | 14% | 3% | 0% | 7% | 7% | 3% |
| Large | 0% | 0% | 21% | 0% | 7% | 14% | 0% | 3% | 14% |
| Kappa | 0.79 (0.57, 1.00)† | 0.57 (0.27, 0.88)† | 0.71 (0.45, 0.97)† |
| **Inconsistency factor (log odd ratio)** |
|  | Common-within-network | Trial-specific | Intervention-specific |
| *Strength of evidence*1 |
| IDE | Weak | Strong | Weak | Strong | Weak | Strong |
| Weak | 94% | 0% | 94% | 0% | 94% | 1% |
| Strong | 0% | 6% | 0% | 6% | 1% | 4% |
| Kappa | 1.00 | 1.00 | 0.85 (0.64, 1.00)† |
| *Direction of evidence*2 |
| IDE | Positive  | Negative | Positive  | Negative | Positive  | Negative |
| Positive | 48% | 1% | 46% | 0% | 47% | 1% |
| Negative | 0% | 51% | 0% | 54% | 0% | 52% |
| Kappa | 0.97 (0.93, 1.00)\* | 1.00 | 0.98 (0.96, 1.00)\* |

IDE: identical; LA: large; LO: low; MO: moderate.

1Strong evidence when 0 (in the log scale) is not included in the 95% credible interval, otherwise weak evidence.

2Whether the estimated log odds ratio favors the first or second intervention in a comparison. In case of inconsistency factor, whether the difference between direct and indirect estimate for a specific comparison is positive or negative.

3Estimated between-trial variance is low, moderate and large when it is smaller than the median, between the median and 3rd quartile and larger than the 3rd quartile, respectively, of the selected empirical distribution for the true between-trial variance.

\*Almost perfect agreement (0.81 – 1.00);

†95% confidence interval is too wide to judge the level of agreement with confidence.

|  |
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| **Agreement among different structures of prior distribution on log IMOR** |

**Identical structure**

**Table S7. Agreement on direction, strength of evidence and extent of heterogeneity**

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| --- |
| **Basic parameters (log odds ratio)** |
|  | Common *vs*. Intervention | Common *vs*. Trial | Intervention *vs*. Trial |
| *Strength of evidence*1 |
|  | Weak | Strong | Weak | Strong | Weak | Strong |
| Weak  | 57% | 0% | 55% | 2% | 55% | 6% |
| Strong | 4% | 39% | 1% | 42% | 1% | 38% |
| Kappa | 0.91 (0.85, 0.97)\* | 0.95 (0.91, 1.00)\* | 0.86 (0.79, 0.94)\* |
| *Direction of evidence*2 |
|  | First | Second | First | Second | First | Second |
| First | 86% | 1% | 86% | 0% | 86% | 0% |
| Second | 0% | 14% | 0% | 14% | 1% | 14% |
| Kappa | 0.98 (0.93, 1.00)\* | 1.00 | 0.98 (0.93, 1.00)\* |
| *Extent of between-trial variance*3 |
|  | LO | MO | LA | LO | MO | LA | LO | MO | LA |
| Low | 62% | 0% | 0% | 62% | 0% | 0% | 62% | 3% | 0% |
| Moderate | 3% | 14% | 0% | 0% | 17% | 0% | 0% | 14% | 3% |
| Large | 0% | 3% | 17% | 0% | 0% | 21% | 0% | 0% | 17% |
| Kappa | 0.87 (0.69, 1.00)† | 1.00 | 0.87 (0.69, 1.00)† |
| **Inconsistency factor (log odd ratio)** |
|  | Common *vs*. Intervention | Common *vs*. Trial | Intervention *vs*. Trial |
| *Strength of evidence*1 |
|  | Weak | Strong | Weak | Strong | Weak | Strong |
| Weak | 94% | 0% | 94% | 0% | 94% | 1% |
| Strong | 1% | 5% | 0% | 6% | 0% | 5% |
| Kappa | 0.93 (0.79, 1.00)\* | 1.00 | 0.93 (0.79, 1.00)\* |
| *Direction of evidence*2 |
|  | Positive  | Negative | Positive  | Negative | Positive  | Negative |
| Positive | 48% | 1% | 46% | 2% | 46% | 1% |
| Negative | 0% | 51% | 0% | 51% | 0% | 52% |
| Kappa | 0.98 (0.96, 1.00)\* | 0.96 (0.91, 1.00)\* | 0.97 (0.93, 1.00)\* |

Common: common-within-network; Intervention: intervention-specific; LA: large; LO: low; MO: moderate; Trial: trial-specific.

1Strong evidence when 0 (in the log scale) is not included in the 95% credible interval, otherwise weak evidence.

2Whether the estimated log odds ratio favors the first or second intervention in a comparison. In case of inconsistency factor, whether the difference between direct and indirect estimate for a specific comparison is positive or negative.

3Estimated between-trial variance is low, moderate and large when it is smaller than the median, between the median and 3rd quartile and larger than the 3rd quartile, respectively, of the selected empirical distribution for the true between-trial variance.

\*Almost perfect agreement (0.81 – 1.00);

†95% confidence interval is too wide to judge the level of agreement with confidence.

**Hierarchical structure**

**Table S8. Agreement on direction, strength of evidence and extent of heterogeneity**

|  |
| --- |
| **Basic parameters (log odds ratio)** |
|  | Common *vs*. Intervention | Common *vs*. Trial | Intervention *vs*. Trial |
| *Strength of evidence*1 |
|  | Weak | Strong | Weak | Strong | Weak | Strong |
| Weak  | 58% | 0% | 57% | 1% | 58% | 3% |
| Strong | 3% | 39% | 1% | 41% | 1% | 39% |
| Kappa | 0.94 (0.89, 0.99)\* | 0.95 (0.91, 1.00)\* | 0.92 (0.86 0.98)\* |
| *Direction of evidence*2 |
|  | First | Second | First | Second | First | Second |
| First | 85% | 1% | 86% | 0% | 85% | 0% |
| Second | 0% | 14% | 0% | 14% | 1% | 14% |
| Kappa | 0.95 (0.89, 1.00)\* | 1.00 | 0.95 (0.89, 1.00)\* |
| *Extent of between-trial variance*3 |
|  | LO | MO | LA | LO | MO | LA | LO | MO | LA |
| Low | 72% | 0% | 0% | 72% | 0% | 0% | 72% | 0% | 0% |
| Moderate | 0% | 7% | 0% | 3% | 3% | 0% | 3% | 7% | 0% |
| Large | 0% | 3% | 17% | 0% | 7% | 14% | 0% | 3% | 14% |
| Kappa | 0.92 (0.77, 1.00)† | 0.75 (0.48, 1.00)† | 0.75 (0.48, 1.00)† |
| **Inconsistency factor (log odd ratio)** |
|  | Common *vs*. Intervention | Common *vs*. Trial | Intervention *vs*. Trial |
| *Strength of evidence*1 |
|  | Weak | Strong | Weak | Strong | Weak | Strong |
| Weak | 94% | 0% | 94% | 0% | 94% | 1% |
| Strong | 1% | 5% | 0% | 6% | 0% | 5% |
| Kappa | 0.93 (0.79, 1.00)\* | 1.00 | 0.93 (0.79, 1.00)\* |
| *Direction of evidence*2 |
|  | Positive  | Negative | Positive  | Negative | Positive  | Negative |
| Positive | 47% | 0% | 46% | 1% | 46% | 1% |
| Negative | 0% | 53% | 0% | 53% | 0% | 53% |
| Kappa | 1.00 | 0.98 (0.96, 1.00)\* | 0.98 (0.96, 1.00)\* |

Common: common-within-network; Intervention: intervention-specific; LA: large; LO: low; MO: moderate; Trial: trial-specific.

2Whether the estimated log odds ratio favors the first or second intervention in a comparison. In case of inconsistency factor, whether the difference between direct and indirect estimate for a specific comparison is positive or negative.

3Estimated between-trial variance is low, moderate and large when it is smaller than the median, between the median and 3rd quartile and larger than the 3rd quartile, respectively, of the selected empirical distribution for the true between-trial variance.

\*Almost perfect agreement (0.81 – 1.00);

†95% confidence interval is too wide to judge the level of agreement with confidence.

|  |
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| **Agreement between pattern-mixture model and selection model** |

**Table S9. Agreement on direction, strength of evidence and extent of heterogeneity**

|  |
| --- |
| **Basic parameters (log odds ratio)** |
|  | Common within network | Trial-specific | Intervention-specific |
| *Strength of evidence*1 |
| Pattern | Weak | Strong | Weak | Strong | Weak | Strong |
| Weak  | 56% | 1% | 55% | 1% | 61% | 1% |
| Strong | 1% | 42% | 1% | 43% | 1% | 38% |
| Kappa | 0.96 (0.91, 1.00)\* | 0.97 (0.93, 1.00)\* | 0.96 (0.93, 1.00)\* |
| *Direction of evidence*2 |
| Pattern | First | Second | First | Second | First | Second |
| First | 85% | 1% | 86% | 1% | 85% | 1% |
| Second | 0% | 14% | 0% | 14% | 0% | 14% |
| Kappa | 0.95 (0.89, 1.00)\* | 0.98 (0.93, 1.00)\* | 0.98 (0.95, 1.00)\* |
| *Extent of between-trial variance*3 |
| Pattern | LO | MO | LA | LO | MO | LA | LO | MO | LA |
| Low | 59% | 3% | 0% | 62% | 0% | 0% | 66% | 0% | 0% |
| Moderate | 3% | 14% | 0% | 3% | 14% | 0% | 3% | 10% | 3% |
| Large | 0% | 3% | 17% | 0% | 0% | 21% | 0% | 0% | 17% |
| Kappa | 0.81 (0.60, 1.00)† | 0.93 (0.81, 1.00)\* | 0.86 (0.67, 1.00)† |
| **Inconsistency factor (log odd ratio)** |
|  | Common within network | Trial-specific | Intervention-specific |
| *Strength of evidence*1 |
| Pattern | Weak | Strong | Weak | Strong | Weak | Strong |
| Weak | 94% | 0% | 94% | 0% | 94% | 1% |
| Strong | 1% | 5% | 0% | 6% | 0% | 5% |
| Kappa | 0.93 (0.79, 1.00)\* | 1.00 | 0.87 (0.68, 1.00)† |
| *Direction of evidence*2 |
| Pattern | Positive  | Negative | Positive  | Negative | Positive  | Negative |
| Positive | 49% | 0% | 46% | 0% | 48% | 0% |
| Negative | 0% | 51% | 1% | 53% | 1% | 51% |
| Kappa | 1.00 | 0.98 (0.96, 1.00)\* | 0.98 (0.96, 1.00)\* |

Common: common-within-network; Intervention: intervention-specific; LA: large; LO: low; MO: moderate; Trial: trial-specific.

1Strong evidence when 0 (in the log scale) is not included in the 95% credible interval, otherwise weak evidence.

2Whether the estimated log odds ratio favors the first or second intervention in a comparison. In case of inconsistency factor, whether the difference between direct and indirect estimate for a specific comparison is positive or negative.

3Estimated between-trial variance is low, moderate and large when it is smaller than the median, between the median and 3rd quartile and larger than the 3rd quartile, respectively, of the selected empirical distribution for the true between-trial variance.

\*Almost perfect agreement (0.81 – 1.00);

†95% confidence interval is too wide to judge the level of agreement with confidence.

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| --- |
| **Agreement between moderate and other prior variances for log IMOR** |

**Table S10. Agreement on direction, strength of evidence and extent of heterogeneity**

|  |
| --- |
| **Basic parameters (log odds ratio)** |
|  | Conservative | Liberal |
| *Strength of evidence*1 |
| Moderate | Weak | Strong | Weak | Strong |
| Weak  | 61% | 0% | 60% | 2% |
| Strong | 2% | 37% | 1% | 38% |
| Kappa | 0.96 (0.93, 1.00)\* | 0.95 (0.91, 1.00)\* |
| *Direction of evidence*2 |
| Moderate | First | Second | First | Second |
| First | 84% | 2% | 86% | 0% |
| Second | 0% | 14% | 1% | 14% |
| Kappa | 0.93 (0.86, 1.00)\* | 0.98 (0.93, 1.00)\* |
| *Extent of between-trial variance*3 |
| Moderate | LO | MO | LA | LO | MO | LA |
| Low | 62% | 3% | 0% | 62% | 3% | 0% |
| Moderate | 3% | 14% | 0% | 3% | 14% | 3% |
| Large | 0% | 3% | 14% | 0% | 0% | 17% |
| Kappa | 0.80 (0.58, 1.00)† | 0.87 (0.69, 1.00)† |
| **Inconsistency factor (log odd ratio)** |
|  | Conservative | Liberal |
| *Strength of evidence*1 |
| Moderate | Weak | Strong | Weak | Strong |
| Weak | 94% | 1% | 94% | 1% |
| Strong | 1% | 4% | 0% | 5% |
| Kappa | 0.70 (0.41, 0.99)† | 0.93 (0.79, 1.00)\* |
| *Direction of evidence*2 |
| Moderate | Positive  | Negative | Positive  | Negative |
| Positive | 47% | 1% | 48% | 0% |
| Negative | 0% | 52% | 1% | 51% |
| Kappa | 0.98 (0.96, 1.00)\* | 0.99 (0.96, 1.00)\* |

Conservative: variance equal 4; LA: large; Liberal: variance equal 0.25; LO: low; MO: moderate; Moderate: variance equal 1.

1Strong evidence when 0 (in the log scale) is not included in the 95% credible interval, otherwise weak evidence.

2Whether the estimated log odds ratio favors the first or second intervention in a comparison. In case of inconsistency factor, whether the difference between direct and indirect estimate for a specific comparison is positive or negative.

3Estimated between-trial variance is low, moderate and large when it is smaller than the median, between the median and 3rd quartile and larger than the 3rd quartile, respectively, of the selected empirical distribution for the true between-trial variance.

\*Almost perfect agreement (0.81 – 1.00);

†95% confidence interval is too wide to judge the level of agreement with confidence.

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| **Judging the extraction accuracy of the analySed networks** |

**Table S11. Judgment of accuracy extraction of the eligible networks with justifications**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ID | Information on outcome of completers for all included trials | Information on outcome “withdrawal” for all included trials | Explicit description of how missing outcome data are handled in NMA | Extraction accuracy | Notes |
| 1 |  | x | x | Unclear | LOCF has been already employed in some of the trials. |
| 2 |  | x |  | Unacceptable | In Table 1, in some trials the analysed for Response is equal to or smaller than the analysed for Withdrawals. Outcomes might have been extracted and analysed as reported. |
| 3 |  | x |  | Unacceptable | The reviewers excluded trials without ITT in a sensitivity analysis. Therefore, they might have analysed the outcomes as reported in the trials |
| 4 |  | x |  | Unacceptable | 'Analyses were carried out for the intention to treat (ITT) '. Results are provided narratively without tabulation of the study results in order to understand how many were analysed out of the total randomised. |
| 5 |  | x |  | Unacceptable | In Table 1, totals under Efficacy and Acceptability are the same in some trials but smaller in the former in other trials. Probably the reviewers extracted the data as reported in trials.  |
| 6 |  | x |  | Unacceptable | In Table 2, number analysed is smaller than randomised (NPts FAS) in same trials; No information on how each trials handled MOD; no information on how the reviewers handled MOD. |
| 7 |  | x |  | Unacceptable | By comparing Figure 1 with Figure 2 and account for the information on ITT/PP in Table S1, some trials did ITT (no further information) and other analysed as ACA. |
| 8 |  | x |  | Unacceptable | By comparing the totals in the efficacy outcome with those in the DO outcome, we might infer that ITT with imputation has been done; The reviewers reported that they planned ITT. |
| 9 |  | x | x | Unclear | 'We observe that, for all but EOP 1003 and EOP 1004 studies, one important limitation was that we could extract data reported with the Last Observation Carried Forward (LOCF) technique to account for missing data, although we attempted an available case extraction from material on FDA website yielding incomplete data collection.' Table 1 presents the sample analysed and the MOD frequency per arm. |
| 10 |  | x |  | Unacceptable | The reviewers report that they employed ITT but without further information; It is has been explicitly reported that each trial applied ITT. |
| 11 |  | x | x | Unclear | The reviewers explicitly reported than ITT was applied and by comparing totals reported in the Table of Characteristics with those in Analysis 1.1, we conclude that ITT might have been indeed applied |
| 12 |  | x |  | Unacceptable | Table 1 reports ITT, but the totals in Figure 2 (primary outcome) are smaller than the totals in Figure 3 (DO) for some trials. Probably outcomes extracted (and analysed) as reported in the trials. |
| 13 |  | x |  | Unacceptable | By comparing the totals in the dropout outcome (Figure 2C) with the totals in the primary outcome (Figure 2A), the latter are smaller. Probably ACA was employed. |
| 14 |  | x |  | Unacceptable | In Appendix Table S1, by comparing the total of the primary outcome (response) with the total in the DO, we see that some trials may have employed ITT whereas others ACA. Probably outcomes extracted (and analysed) as reported in the trials. |
| 15 |  | x |  | Unacceptable | Table 1 refers to Q6 'Were all analyses carried out using data from the Intention To Treat (ITT) patient group?'. Probably outcomes extracted (and analysed) as reported in the trials. |
| 16 |  | x |  | Unacceptable | Compare Appendix B (it gives information on randomised and completers’ sample) with Table 1: totals in Table 1 are smaller in all studies. Probably ACA was employed. |
| 17 |  | x |  | Unacceptable | No distinction on the analysed and randomised sample for each trial; no information on how MOD have been handled in each trial. |
| 18 |  | x | x | Unclear | Table e4 (information on number randomised) agrees with Table e2 (efficacy outcome) and Table e4 (acceptability) in terms of total analysed but no distinction is made between completers and MOD. Imputation under AMF scenario. |
| 19 |  | x |  | Unacceptable | There is explicit information on Supplemental Table 6 on the statistical method employed in the trials but the reviewers do not reported how they handled MOD.  |
| 20 |  | x |  | Unacceptable | Table S1 provides information on the analysed sample for the primary outcome and the DO. These samples are the same in some trials, whereas smaller in the former in others. Possible outcome extracted and analysed as reported in the trials. |
| 21 |  | x |  | Unacceptable | No distinction on the analysed and randomised sample for each trial; no information on how MOD have been handled in each trial; reviewers don’t report how they planned to handle MOD. |
| 22 |  | x |  | Unacceptable | Number randomised has been also analysed, by comparing the Table of characteristics and the information on attrition bias with the analysed outcome. The reviewers do not mention how they handled MOD. |
| 23 |  | x |  | Unacceptable | Table 1 explicitly reports how each trial handled MOD for every outcome. Reviewers do not mention how they handled MOD. |
| 24 |  | x | x | Unclear | 'The denominator used in all trials was based on a modified intention-to-treat (mITT) analysis […]'. In Table 1 many studies provide data both in ITT and mITT and others as ITT only. |
| 25 |  | x | x | Unclear | By comparing the totals in the efficacy outcome (Figure S1) with those in the DO (Figure S2), it seems that ITT must have been employed. Imputation under AMF scenario. |
| 26 |  | x |  | Unacceptable | There is information on the analyses and randomised sample for each arm of every trial ('Results – Key information about each identified RCT' in Supplementary material); no information on how MOD were handled. |
| 27 |  | x |  | Unacceptable | By comparing the analyses totals (Analysis 1, Comparison 1) with the randomised total in RoB table it is obvious that the reviewers applied genuine ITT, but without information on how reviewers handled MOD. |
| 28 |  | x |  | Unacceptable | No distinction between randomised and analysed sample; no information on how MOD were addressed. |
| 29 |  | x |  | Unacceptable | The reviewers analysed the data as reported ''All studies considered non-completion as failure and reported data for the randomised patients who received at least 1 dose (ie, intent-to-treat exposed population), except for the study by Riddler et al, which ignored missing data''. Combination of ITT, modified-TT and ACA. |

References of the analysed reviews are provided below e-Table2