Supplementary Online Content

Mitra S, Florez ID, Tamayo ME, et al. Association of placebo, indomethacin, ibuprofen, and acetaminophen with closure of hemodynamically significant patent ductus arteriosus in preterm infants: a systematic review and meta-analysis. *JAMA*. doi:10.1001/jama.2018.1896

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

Table of contents for Supplement 3

eTable 1. Glossary of abbreviations, acronyms (including dosage & routes of administration of medications) and terms

Abbreviations
• PDA: Patent ductus arteriosus • Hs-PDA: hemodynamically-significant PDA • CENTRAL: Cochrane Central Register of Controlled Trials • NEC: Necrotizing enterocolitis • BPD: bronchopulmonary dysplasia • IVH: Intraventricular hemorrhage • RCT: Randomized Controlled Trial • OR: Odds ratio • CrI: Credible interval • SUCRA: Surface under the cumulative ranking • PROSPERO: International prospective register of systematic reviews • DA: ductus arteriosus • NMA: Network meta-analysis • ISPOR: International Society For Pharmacoeconomics and Outcomes Research • PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses • ECHO: echocardiography • RoB: Risk of Bias • RE: Random effects • DBT: Design by treatment • GRADE: Grading of Recommendations Assessment, Development and Evaluation • RR: Relative Risk • CI: Confidence intervals • AUC: Area under the curve • BW: Birth weight • GA: Gestational age
Acronyms for pharmacotherapeutic options (with routes & doses)
• INDOIV: Intravenous (IV) indomethacin standard dose (0.1-0.3 mg/kg IV every 12-24h for a total of 3 doses) • IBUIV: Intravenous ibuprofen standard dose (10 mg/kg IV followed by 5mg/kg IV every 12-24 h for a total of 3 doses) • IBUPO: Oral ibuprofen standard dose (10 mg/kg oral followed by 5mg/kg oral every 12-24 h for a total of 3 doses) • PARAPO: Oral acetaminophen 15 mg/kg/dose four times a day for 3-7 days • IBUPOHIGHDOSE: Oral ibuprofen high dose (15-20 mg/kg oral followed by 7.5-10 mg/kg oral every 12-24 h for a total of 3 doses) • IBUIVHIGHDOSE: Intravenous ibuprofen high dose (15-20 mg/kg IV followed by 7.5-10 mg/kg IV every 12-24 h for a total of 3 doses) • INDOIVCONT: Intravenous indomethacin infused continuously for 36 h at a rate of 17 mcg/kg/h • IBUIVCONT: Intravenous ibuprofen continuous infusions of 10mg/kg (0.416 mg/kg/h), 5 mg/kg (0.208 mg/kg/h) and 5 mg/kg(0.208 mg/kg/h), and boluses of equal volumes of 5% dextrose administered over 15 min, 24 h apart • INDOPO: Oral indomethacin standard dose (dose same as INDOIV) • INDOIVHIGHDOSE: Intravenous indomethacin 0.2-0.5mg/kg every day for 3 days • INDOIVPROLONGED: Intravenous indomethacin prolonged treatment course (0.1-0.15 mg/kg every 12-24 h for 5-7 days). • INDOIVLATE: Intravenous indomethacin standard dose (dose same as INDOIV); late initiation of therapy (started on or beyond day 7) • INDOIVFRU: Intravenous indomethacin standard dose (dose same as INDOIV) along with Frusemide • INDOIVECHOGUIDED: Intravenous indomethacin standard dose (dose same as INDOIV); duration guided by echo assessment of PDA • INDOTHERS: Indomethacin, other types (INDOPO + INDOIVLATE + INDOIVFRU + INDOIVECHOGUIDED + INDOIVHIGHDOSE + INDOIVPROLONGED) • PLAC: Placebo • NORX: No treatment • PLAC_NORX: Placebo + No treatment

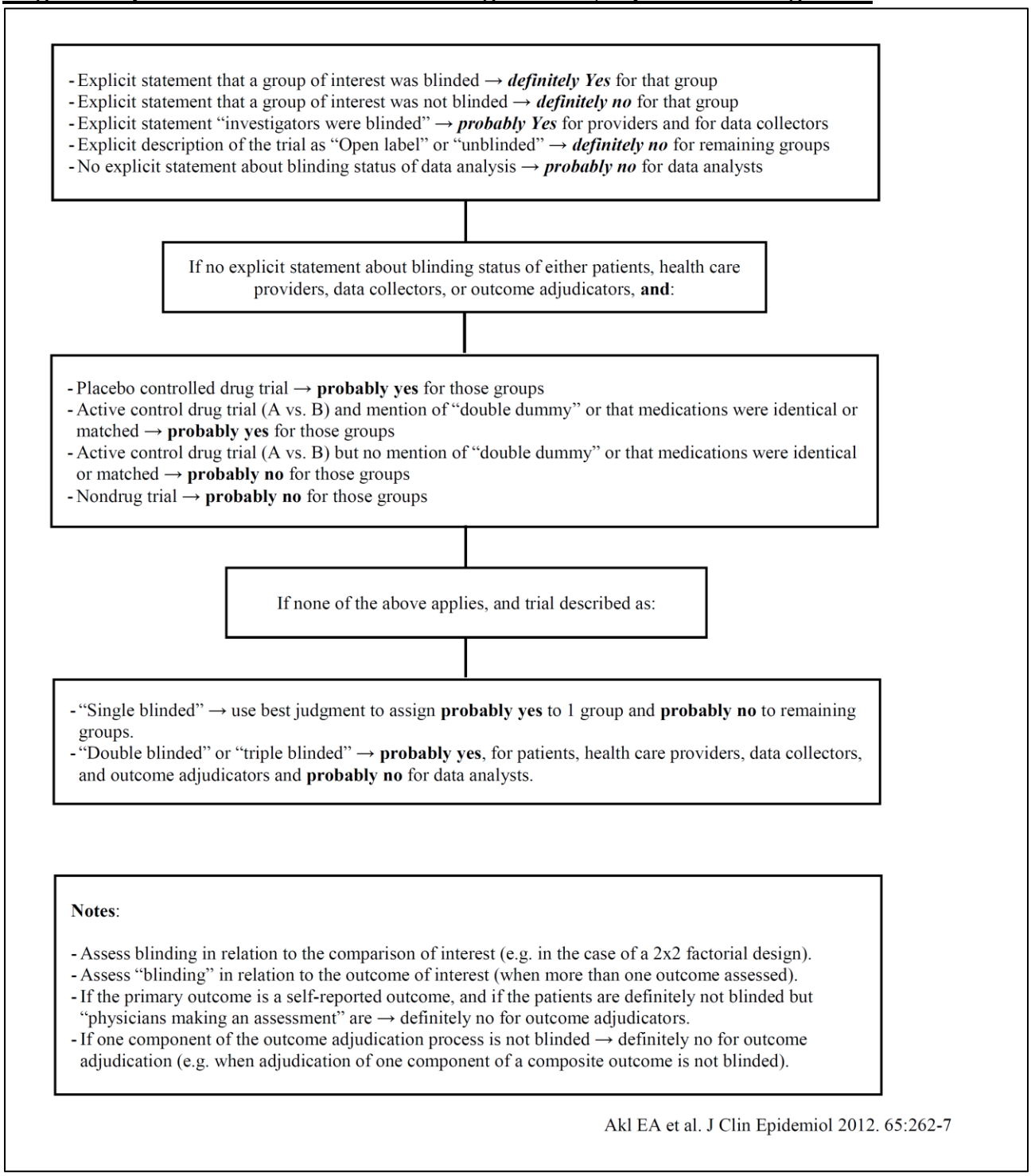
eTable 2. Electronic Database Search Strategies

MEDLINE (on OVID platform)	EMBASE (on OVID platform)	CENTRAL (Cochrane Central Register of Controlled Trials)
1. Infant, Premature/ or Premature Birth/ or Infant, Newborn/ or Infant, Premature, Diseases/ or preterm.mp. 2. low birth weight.mp. or Infant, Low Birth Weight/ 3. very low birth weight.mp. or Infant, Very Low Birth Weight/ 4. Infant, Extremely Low Birth Weight/ 5. 1 or 2 or 3 or 4 6. Ductus Arteriosus, Patent/ 7. patent ductus arteriosus.mp. 8. ductus arteriosus.mp. or Ductus Arteriosus/ 9. ductus.mp. 10. PDA.mp. 11. persistent ductus arteriosus.mp. 12. 6 or 7 or 8 or 9 or 10 or 11 13. indomethacin.mp. or Indomethacin/ 14. indometacin.mp. 15. indocid.mp. 16. ibuprofen.mp. or Ibuprofen/ 17. brufen.mp. 18. paracetamol.mp. or Acetaminophen/ 19. tylenol.mp. 20. Anti-Inflammatory Agents, Non-Steroidal/ 21. Cyclooxygenase Inhibitors/ or prostaglandin synthetase inhibitor.mp. 22. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 23. 5 and 12 and 22 24. Randomized Controlled Trial/ 25. randomized controlled trials.mp. 26. Random Allocation/ 27. Double-Blind Method/ 28. Single-Blind Method/ 29. Clinical Trial/ 30. clinical trial,phase i.pt. 31. clinical trial,phase ii.pt. 32. clinical trial,phase iii.pt. 33. clinical trial,phase iv.pt. 34. controlled clinical trial.pt. 35. randomized controlled trial.pt. 36. multicenter study.pt. 37. clinical trial.pt. 38. Clinical Trial/ 39. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 40. (clinical adj trial$).tw. 41. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. 42. PLACEBOS/ 43. placebo$.tw. 44. randomly allocated.tw. 45. allocated adj2 random$).tw. 46. 40 or 41 or 42 or 43 or 44 or 45 47. 39 or 46 48. case report.tw. 49. letter/ 50. historical article/ 51. 48 or 49 or 50 52. 47 not 51 53. 23 and 52	1. Infant, Premature/ 2. Premature Birth/ 3. Infant, Newborn/ 4. Infant, Premature, Diseases/ 5. preterm.mp. 6. low birth weight.mp. 7. Infant, Low Birth Weight/ 8. very low birth weight.mp. 9. Infant, Extremely Low Birth Weight/ 10. lbw.mp. 11. vlbw.mp. 12. or/1-11 13. Ductus Arteriosus, Patent/ 14. patent ductus arteriosus.mp. 15. ductus arteriosus.mp. 16. Ductus Arteriosus/ 17. ductus.mp. 18. PDA.mp. 19. persistent ductus arteriosus.mp. 20. or/13-19 21. indomethacin.mp. 22. Indomethacin/ 23. indometacin.mp. 24. indocid.mp. 25. ibuprofen.mp. 26. Ibuprofen/ 27. brufen.mp. 28. paracetamol.mp. 29. Acetaminophen/ 30. tylenol.mp. 31. acetaminophen.mp. 32. Anti-Inflammatory Agents, Non-Steroidal/ 33. Cyclooxygenase Inhibitors/ 34. prostaglandin synthetase inhibitor.mp. 35. NSAID?.mp. 36. or/21-35 37. 12 and 20 and 36 38. Randomized Controlled Trial/ 39. randomized controlled trials.mp. 40. Random Allocation/ 41. Double-Blind Method/ 42. Single-Blind Method/ 43. Clinical Trial/ 44. randomized controlled trial.pt. 45. clinical trial.pt. 46. Clinical Trial/ 47. or/38-46 48. (clinical adj trial$).tw. 49. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. 50. PLACEBOS/ 51. placebo$.tw. 52. randomly allocated.tw. 53. (allocated adj2 random$).tw. 54. or/48-53 55. 47 or 54 56. 37 and 55	#1 infant, premature #2 Premature Birth #3 Infant, Newborn #4 Infant, Premature, Diseases #5 preterm.mp. #6 low birth weight.mp. #7 Infant, Low Birth Weight #8 very low birth weight.mp. #9 Infant, Extremely Low Birth Weight #10 lbw.mp. #11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 #12 Ductus Arteriosus, Patent #13 Ductus Arteriosus #14 PDA.mp. #15 #12 or #13 or #14 #16 Indomethacin #17 indomethacin.mp. #18 indometacin.mp. #19 ibuprofen.mp. #20 Ibuprofen #21 brufen.mp. #22 paracetamol.mp. #23 Acetaminophen #24 tylenol.mp. #25 Anti-Inflammatory Agents, Non-Steroidal #26 Cyclooxygenase Inhibitors #27 prostaglandin synthetase inhibitor.mp. #28 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 #29 #11 and #15 and #28

eText 1. Risk of Bias Assessment of eligible studies

The risk of bias of eligible studies was assessed according to a modified and validated version of the Cochrane Collaboration's ROB tool (1). The six criteria that were assessed included sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of follow up, selective outcome reporting, and presence of other biases. Each domain was assigned a score of 'definitely low risk', or 'definitely high risk' or 'unclear risk'. 'Unclear risk' was further categorized to 'probably low risk', or 'probably high risk' based on specific instructions provided to the reviewers provided in the flow diagram below (eFigure 1) (2). This has been adapted from the tool validated by Akl et al (2). Two independent reviewers assessed the risk of bias. Disagreements between two reviewers when assessing the risk of bias was resolved through consensus. If a consensus was not reached, the disagreement was resolved by a third reviewer.

eFigure 1. Specific instructions for estimating unclearly reported blinding status



eTable 3. LIST OF EXCLUDED STUDIES after full text screening

No.	Study Reference	Reason for exclusion
1	Amoozgar H, Ghodstehrani M, Pishva N. Oral ibuprofen and ductus arteriosus closure in full-term neonates: A prospective case–control study. Pediatr Cardiol. 2010;1;31(1):40-3.	Not RCT
2	Bravo MD, Cabañas F, Pérez-Fernández E, Quero J, Pellicer A. 212 Randomized Clinical Trial on Echocardiographically Guided (ECHOG) Versus Standard Ibuprofen Treatment (SIBT) for Patent Ductus Arteriosus (PDA): Pilot Study. J Neonatal Perinatal Med. 2011;4(3):287-288.	Duplicate (Conference abstract of included study)
3	Brecht M, Wiese M, Hopkins AM, Wojiechowski J, Suppiah V, Garg A, Garg S, Stark MJ, Andersen CC. Pharmakokinetics And Clinical Effects Of A Novel Dosing Regimen For Intravenous Ibuprofen–A Pilot Study. J Paediatr Child Health. 2015;51:97.	Not RCT
4	Carmo KB, Evans N, Paradisis M. Duration of indomethacin treatment of the preterm patent ductus arteriosus as directed by echocardiography. J Pediatr. 2009;155(6):819-22.	Not relevant intervention
5	Clyman RI, Roman C. The effects of caffeine on the preterm sheep ductus arteriosus. Pediatr Res. 2007;62(2):167-9.	Not RCT
6	Dani C, Bertini G, Reali MF, Murru P, Fabris C, Vangi V, Rubaltelli FF. Prophylaxis of patent ductus arteriosus with ibuprofen in preterm infants. Acta Paediatr. 2000;89(11):1369-74.	Prophylactic use of Ibuprofen
7	Desfrere L, Zohar S, Morville P, Brunhes A, Chevret S, Pons G, Moriette G, Rey E, Treluyer JM. Dose-finding study of ibuprofen in patent ductus arteriosus using the continual reassessment method. J Clin Pharm Ther. 2005;30(2):121-32.	Not RCT
8	Eras Z, Gokmen T, Erdeve O, Ozyurt BM, Saridas B, Dilmen U. Impact of oral versus intravenous ibuprofen on neurodevelopmental outcome: a randomized controlled parallel study. Am J Perinat. 2013;30(10):857-62.	Duplicate (Secondary analysis of included study)
9	Eras Z, Gokmen T, Erdeve O, Sarıdas B, Canpolat E, Dilmen U. 1244 Impact of Oral Versus Intravenous Ibuprofen on Neurodevelopmental Outcome: a Randomised Controlled Parallel Study. Arch Dis Child. 2012;97(Suppl 2):A355.	Duplicate (Conference abstract of included study)
10	Lai TH, Soong WJ, Hwang B. Indomethacin for the prevention of symptomatic patent ductus arteriosus in very low birth weight infants. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi. 1990 Jan-Feb;31(1):17-23.	Prophylactic use of Indomethacin
11	Fajardo CA, Whyte RK, Steele BT. Effect of dopamine on failure of indomethacin to close the patent ductus arteriosus. J Pediatr. 1992;121(5):771-5.	Not relevant intervention
12	Gokmen T. Erdeve O, Altug N, Oguz SS, Uras N, Dilmen U. Efficacy and safety of oral versus intravenous ibuprofen in very-low-birth-weight preterms with patent ductus arteriosus. 2010;86:S38.	Duplicate (Conference abstract of included study)
13	Hammerman C, Aramburo MJ. Prolonged indomethacin therapy for the prevention of recurrences of patent ductus arteriosus. 1990. 117(5):771-776.	Not relevant intervention
14	Jannatdoust A, Samadi M, Yeganehdoust S, et al. Effects of intravenous indomethacin on reduction of symptomatic patent ductus arteriosus cases and decreasing the need for prolonged mechanical ventilation. J Cardiovasc Thorac Res. 2014;6(4):257-259.	Prophylactic use of Indomethacin
15	Kluckow M, Evans N, Gill A, Jeffery M. Ductal echocardiographic targeting and early closure trial (DETECT): A pilot randomised controlled trial. 2012;48:43-44.	Duplicate (Conference abstract of included study)
16	Gimeno A, Modesto,V. Comparison of ibuprofen and indomethacin therapy for the treatment of patent ductus arteriosus. Anales de Pediatria Continuada. 2007;5(2):100-104.	Not RCT
17	Gournay V, Roze JC, Kuster A, et al. Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial. Lancet. 2004;364(9449):1939-44.	Prophylactic use of Ibuprofen
18	Hammerman C, Shchors I, Schimmel MS, Bromiker R, Kaplan M, Nir A. N-terminal-pro-B-type natriuretic peptide in premature patent ductus arteriosus: a physiologic biomarker, but is it a clinical tool? Pediatr Cardiol. 2010;31(1):62-5.	Duplicate (Secondary analysis of included study)
19	Mahony L, Carnero V, Brett C, Heymann MA, Clyman RI. Prophylactic indomethacin therapy for patent ductus arteriosus in very-low-birth-weight infants. N Engl J Med. 1982;306(9):506-10.	Prophylactic use of Indomethacin

eTable 3. LIST OF EXCLUDED STUDIES after full text screening (continued)		
No.	**Study Reference**	**Reason for exclusion**
20	Mardoum R, Bejar R, Merritt TA, Berry C. Controlled study of the effects of indomethacin on cerebral blood flow velocities in newborn infants. J Pediatr. 1991;118(1):112-5.	Not relevant outcome
21	Maruyama K, Fujiu T. Effects of prophylactic indomethacin on renal and intestinal blood flows in premature infants. Pediatr Int. 2012;54(4):480-5.	Prophylactic use of Indomethacin
22	Nestrud R. Hil D. Arrington,R. A double blind controlled study on the efficacy of indomethacin (Ind) in closure of patent ductus arteriosus (PDA) in premature infants. Ped Res. 1979;13(4, Part II):14.	Duplicate (Conference abstract of included study)
23	Van Overmeire B, Allegaert K, Casaer A, et al. Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2004;364(9449):1945-9.	Prophylactic use of Ibuprofen
24	Schmidt B, Roberts RS, Fanaroff A, et al. TIPP Investigators. Indomethacin prophylaxis, patent ductus arteriosus, and the risk of bronchopulmonary dysplasia: further analyses from the Trial of Indomethacin Prophylaxis in Preterms (TIPP). J Pediatr. 2006;148(6):730-734.	Not RCT
25	Supapannachart S, Khowsathit P, Patchakapati B. Indomethacin prophylaxis for patent ductus arteriosus (PDA) in infants with a birth weight of less than 1250 grams. J Med Assoc Thai. 1999;82 Suppl 1:S87-92.	Prophylactic use of Indomethacin
26	Valaes T, Moylan F, Cohn H. Incidence and significance of PDA in preterm infants (PTI) and controlled blind trial of indomethacin (IND). Ped Res. 1980;14(4, Part II):15.	Not relevant population
27	Van Overmeire B. The use of ibuprofen in neonates in the treatment of patent ductus arteriosus. Int J Clin Pract Suppl. 2003;(135):23-7.	Duplicate (Commentary on included study)
28	Vargas-Origel A, Cruz-Anguiano V, López-Montaño E. [Indomethacin and furosemide in closure of ductus arteriosus]. Bol Med Hosp Infant Mex. 1986;43(8):482-8. [Spanish]	Not relevant outcome
29	Yanowitz TD, Reese J, Gillam-Krakauer M, et al. Superior mesenteric artery blood flow velocities following medical treatment of a patent ductus arteriosus. J Pediatr. 2014;164(3):661-3.	Not relevant intervention/outocme
30	Yanowitz TD, Baker RW, Sobchak Brozanski B. Prophylactic indomethacin reduces grades III and IV intraventricular hemorrhages when compared to early indomethacin treatment of a patent ductus arteriosus. J Perinatol. 2003;23(4):317-22.	Prophylactic use of Indomethacin
31	Yeh TF, Raval D, Lilien LD, Srinivasan G, Pildes RS. Decreased plasma glucose after indomethacin therapy in premature infants with patent ductus anteriosus. Lancet. 1982;2(8289):104-5.	Duplicate (Secondary analysis from included study)
32	Yeh TF, Thalji A, Luken,J. Intravenous indocin therapy in premature infants with PDA: A double-blind control study. Ped Res. 1979; 13(4, Part II):17.	Duplicate (Conference abstract of included study)
33	Zanardo V, Trevisanuto D, Dani C, et al. "Silent" patent ductus arteriosus and bronchopulmonary dysplasia in low birth weight infants. J Perinat Med. 1995;23(6):493-9.	Not RCT
34	Peckham GJ, Miettinen OS, Ellison RC, et al. Clinical course to 1 year of age in premature infants with patent ductus arteriosus: results of a multicenter randomized trial of indomethacin. J Pediatr. 1984;105(2):285-91.	Duplicate (Secondary analysis from included study)
35	Prifti E, Enkeleda P, Rubena M, Alketa H. The impact of antenatal corticosteroids on PDA in low birth weight preterm infants. J Perinatal Med. 2013;41(s1)	Not relevant outcome
36	Weesner KM, Dillard RG, Boyle RJ, Block SM. Prophylactic treatment of asymptomatic patent ductus arteriosus in premature infants with respiratory distress syndrome. South Med J. 1987;Jun;80(6):706-8.	Prophylactic use of Indomethacin
37	Yeh TF, Goldbarg HR, Henek T, Thalji A, Pildes RS. Intravenous indomethacin therapy in premature infants with patent ductus arteriosus. Causes of death and one-year follow-up. Am J Dis Child. 1982;136(9):803-7.	Duplicate (Secondary analysis from included study)
38	Yeh TF, Raval D, Pyati S, Pildes RS. Retinopathy of prematurity (ROP) and indomethacin therapy in premature infants with patent ductus arteriosus (PDA). Prostaglandins. 1983;25(3):385-91.	Not relevant outcome
39	Yeh TF, Thalji A, Luken L, Lilien L, Carr I, Pildes RS. Improved lung compliance following indomethacin therapy in premature infants with persistent ductus arteriosus. Chest. 1981;80(6):698-700.	Duplicate (Secondary analysis from included study)
40	Satar M, Yapicioğlu H, Narli N, Ozbarlas N, Küçükosmanoğlu O, Tutak E. Is oral indomethacin effective in treatment of preterm infants with patent ductus arteriosus? Turk J Pediatr. 2004;46(2):137-41.	Not RCT

eTable 3. LIST OF EXCLUDED STUDIES after full text screening (continued)		
No.	**Study Reference**	**Reason for exclusion**
41	Zanardo V, Vedovato S, Chiozza L, Faggian D, Favaro F, Trevisanuto D. Pharmacological closure of patent ductus arteriosus: effects on pulse pressure and on endothelin-1 and vasopressin excretion. Am J Perinatol. 2008;25(6):353-8.	Not relevant outcome
42	Alipour MR, Mozaffari Shamsi M, Namayandeh SM, Pezeshkpour Z, Rezaeipour F, Sarebanhassanabadi M. The Effects of Oral Ibuprofen on Medicinal Closure of Patent Ductus Arteriosus in Full-Term Neonates in the Second Postnatal Week. Iran J Pediatr. 2016;26(4):e5807.	Not relevant population (full term infants)
43	Demir N, Peker E, Ece İ, Balahoroğlu R, Tuncer O. Efficacy and safety of rectal ibuprofen for patent ductus arteriosus closure in very low birth weight preterm infants. J Matern Fetal Neonatal Med. 2017;30(17):2119-2125.	Not relevant intervention
44	Dorval VG, Martin B, Brassard M, Miro J, Chemtob S, Payot,A. The evolution of serum PGE2 during oral and intravenous ibuprofen treatment in preterm infants with patent ductus arteriosus (PDA). Pediatr Child Health. 2010;15:46A.	Not relevant outcome
45	Knight D, Alkindi S, Buksh M, Kuschel C, Skinner,J. Placebo-controlled pilot trial of indomethacin in preterm infants with a patent ductus arteriosus. J Pediatr Child Health. 2011;47(s1):88	Not relevant outcome
46	Hoxha A, Kola E, Kuneshka N, Tushe E. Oral versus intravenous ibuprofen for the early closure of patent ductus arteriosus in low birth weight preterm infants. European Medical, Health and Pharmaceutical Journal. 2013;6.	Duplicate publication
47	Akbari Asbagh P, Zarkesh MR, Nili F, Nayeri FS, Tofighi Naeem AT. Prophylactic teatment with oral paracetamol for patent ductus arteriosus in preterm infants: A randomized clinical trial. Tehran U Med J. 2015;73(2)86-92.	Prophylactic use of acetaminophen
48	Jasani B, Kabra N, Nanavati RN. Oral paracetamol in treatment of closure of patent ductus arteriosus in preterm neonates. J Postgrad Med. 2013;59(4):312-4.	Not RCT
49	Görk AS, Ehrenkranz RA, Bracken MB. Continuous infusion versus intermittent bolus doses of indomethacin for patent ductus arteriosus closure in symptomatic preterm infants. Cochrane Database Syst Rev. 2008 Jan 23;(1).	Not RCT

eTable 4. Clinical & Methodological Characteristics of Included Studies

eTable 4. Clinical & Methodological Characteristics of Included Studies

Ref No	Author & year of publication	Language of publication	# of infants enrolled	Gestational age at birth (in weeks) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])]	Birth weight (in grams) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])]	Age at start of treatment (days) [Mean [a] (SD [c])/ [Median [b] (IQR [d]/ Range [e])]	Overall assessment of risk of bias	Criteria for diagnosis of hs-PDA	Intervention characteristics (drug: route & dose)	
37	Adamska 2005	Polish	35	INDO 27.6 [a] (2) [c] IBU 27.7 [a] (1.8) [c]	INDO 1003 [a] (192) [c] IBU 1074 [a] (264) [c]	NR	Probably Low	PDA size >1.5mm; LA:AO ratio>1.3	IV Indomethacin 0.2 mg/kg every 12 h x 3doses	IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h
38	Akisu 2001	Turkish	23	INDO 31.9 [a] (1.3) [c] IBU 32.1 [a] (1.2) [c]	INDO 1645 [a] (190) [c] IBU 1706 [a] (187) [c]	INDO 3.5 [a] (0.6) [c] IBU 3.9 [a] (0.5) [c]	Probably High	Echo confirmed hs-PDA; criteria not specified	Oral Indomethacin 0.2 mg/kg every 12 h x 3doses	Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h
39	Aly 2007	English	21	INDO 32.9 [a] (1.6) [c] IBU 31.2 [a] (2.5) [c]	INDO1884 [a] (485) [c] IBU 1521 [a] (398) [c]	NR	Probably Low	Shunting across PDA graded as mild, moderate, and severe according PDA diameter (<1.5, 1.5 to 2, and >2 mm, respectively); treatment criteria not specified	Intravenous indomethacin (3 doses of IV indomethacin 0.2 mg/kg at 12-hour intervals)	Oral Ibuprofen (Initial dose of 10 mg/kg, followed by two doses of 5 mg/kg each)
40	Aranda 2009	English	136	IBU 26.1 [a] (1.3) [c] PLAC 26.2 [a] (1.4) [c]	IBU 798.5 [a] (128.7) [c] PLAC 797.3 [a] (132.8) [c]	IBU 1.5 [a] (0.74)[c] PLAC 1.4 [a] (0.73) [c]	Low	PDA>1.5mm LA/AO ratio of >1.4:1 LV/AO ratio of >2.1:1	Intravenous Ibuprofen 10 mg/kg loading dose followed by 5 mg/kg/d on the 2nd and 3rd day)	Placebo
41	Baenziger 1999	English	32	INDO 28 [a] (3.1) [c] INDO + dopamine 28.5 [a] (2.3) [c]	INDO1220 [a] (305) [c] INDO + dopamine 1115 [a] (252) [c]	INDO 13 [a] (8.3) [c] INDO+ dopamine 11 [a] (7.56) [c]	Probably High	Clinical signs of hs-PDA along with following echo criteria were: (A) Diastolic or systolic-diastolic reverse flow in the main pulmonary artery, PDA, or both, (B) reversed diastolic flow within the descending aorta below the PDA, (C) diastolic anterograde flow in the branches of the pulmonary arteries; (D) LA/AO ratio of >1.3:1	IV Indomethacin 0.2 mg/kg/dose	IV indomethacin 0.2 mg/kg/dose intravenously + Dopamine 4 mcg/kg/min
42	Bagheri 2016	English	129	IBU 31.7 [a] (2.2) [c] PARA 31.5 [a] (2.3) [c]	IBU 1642 [a] (58.5) [c] PARA 1646 (59.1) [c]	IBU 3.4 [a] (2.1) [c] PARA 2.9 [a] (1.3) [c]	Probably Low	PDA>1.5 mm; LA:AO>1.2	Oral high dose Ibuprofen at 20 mg/kg followed by two 10 mg/kg doses at 24h interval	Oral acetaminophen 15 mg/kg every 6 h for 3 days
43	Bagnoli 2013	English	134	IBU 27.4 [a] (2.5) [c] PLAC 27.8 [a] (4) [c]	IBU 989 [a] (326) [c] PLAC 1197 [a] (835) [c]	NR	Probably High	LA/AO ratio of ≥1.4:1 LV/AO ratio of 2.1:1; and/or narrowest PDA diameter >1.5mm Left-to-right shunting of blood and diastolic reversal of blood flow in the aorta.	IV Ibuprofen 10 mg/kg loading doses, followed by 5 mg/kg/d on the 2nd & 3rd day	Placebo
44	Betkerur 1981	English	21	IND 31.1 [a] (0.6) [c] PLAC 29.6 [a] (0.7) [c]	INDO 1395.2 [a] (92.2) [c] PLAC 1134.3 [a] (150.3) [c]	INDO 7.4 [a] (0.6) [c] PLAC 11.9 [a] (2.6) [c]	Probably High	LA:AO ≥ 1.3	IV Indomethacin 0.3 mg/kg/dose	Placebo (IV saline)
45	Cherif 2008	English	64	IBU oral 29.3 [a] (1.2) [c] IBU IV 28.3 [a] (1.1) [c]	IBU oral 1227.2 [b] (188) [d] (600-1470) IBU IV 1197.7 [b] (158) [d] (630-1420)	NR	Low	A left-to-right ductal shunting; LA:AO > 1.6	IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h	Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h
46	Chotigeat 2003	English	30	INDO 29.86 [a] (2.92) [c] IBU 30.8 [a] (2.3) [c]	INDO 1434 [a] (421) [c] IBU 1412 [a] (354) [c]	NR	Probably High	3 of 5 criteria that includes clinical signs and Doppler echo	IV indomethacin (3 doses of IV indomethacin 0.2 mg/kg at 12-hour intervals)	Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h
47	Christmann 2002	English	32	INDO bolus 30.5 [a] (0.5) [c] INDO continuous 29.4 [a] (0.5) [c]	INDO bolus 1424 [a] (150) [c] INDO continuous 1150 [a] (77) [c]	NR	Probably Low	Left to right PDA shunting on Doppler echo along with the following clinical criteria: Unexplained respiratory insufficiency and/or a persistent need of oxygen, bounding peripheral pulses and cardiac enlargement	IV Indomethacin (0.4mg/kg) (Initial dose was 0.2 mg/kg followed by two doses of 0.1 mg/kg at 12 and 36 h)	IV Indomethacin 0.4 mg/kg continuous infusion
48	Dang 2013	English	160	IBU 30.9 [a] (2.2) [c] PARA 31.2 [a] (1.8) [c]	IBU 1531 [a] (453.5) [c] PARA 1591.9 [a] (348.6) [c]	NR	Probably Low	Any one of the following: 1) LA:AO of ≥1.4 in the parasternal long-axis view 2) PDA diameter of ≥1.4 mm/kg body weight 3) left ventricular enlargement 4) Holodiastolic flow reversal in the descending aorta.	Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h	Oral acetaminophen 15 mg/kg every 6 h for 3 days

eTable 4. Clinical & Methodological Characteristics of Included Studies (cont'd….)

Ref No	Author & year of publication	Language of publication	# of infants enrolled	Gestational age at birth (in weeks) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])]	Birth weight (in grams) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])]	Age at start of treatment (days) [Mean [a] (SD [c])]/ [Median [b] (IQR [d]/ Range [e])]	Overall assessment of risk of bias	Criteria for diagnosis of hs-PDA	Intervention characteristics (drug: route & dose)	
49	Dani 2012	English	70	IBU standard dose 26 [a] (1.7) [c] IBU high dose 25.6 [a] (1.8) [c]	IBU standard dose 835 [a] (215) [c] IBU high dose 781 [a] (225) [c]	NR	Low	Echocardiographic demonstration of a ductal left-to-right shunt, with a LA:AO >1.3 or a PDA >1.5 mm	IV Ibuprofen 20 mg/kg, followed by two doses of 10 mg/kg each, after 24 and 48h	IV Ibuprofen initial dose of 10 mg/kg followed by two doses of 5 mg/kg at 24-h intervals
50	Dash 2015	English	73	PARA 28.5 [a] (2.7) [c] INDO 28.9 [a] (2.6) [c]	PARA 989 [a] (299) [c] INDO 1027 [a] (262) [c]	NR	Low	PDA size ≥1.5 mm; Left to right PDA shunt LA:AO ratio > 1.5:1.	IV Indomethacin 0.2 mg/kg/dose once daily for 3 days	Oral Acetaminophen 15 mg/kg/dose four times daily for 7 days (28 doses)
51	Ding 2014	English	72	30.24 [a] (1.49) [c]	1468.64 [a] (447.62) [c]	NR	Probably High	Echo confirmed hs-PDA; criteria not specified	Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg after 24 and 48 h.	Placebo (Oral 5% glucose)
52	Erdeve 2012	English	70	IBU oral 26.4 [a] (1.1) [c] IBU IV 26.3 [a] (1.3) [c]	IBU oral 892 [a] (117) [c] IBU IV 872 [a] (123) [c]	NR	Low	PDA >1.5 mm; LA:AO >1.5; Left-to-right shunting of blood; End-diastolic reversal of blood flow in the aorta or poor cardiac function	IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h	Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h
53	Fakhraee 2007	English	36	INDO 30.9 [a] (2) [c] IBU 31.5 [a] (1.4) [c]	INDO 1522.1 [a] (357.7) [c] IBU 1658.3 [a] (386.6) [c]	NR	Probably High	Left to right shunt; PDA> 1.5 mm; LA:AO>1.6; severe diastolic backflow in the pulmonary trunk and in the aorta	Oral Indomethacin; 3 doses of 0.2 mg/kg at 24 hour intervals	Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h
54	Fesharaki 2012	Persian	60	IBU high dose 29.77 [a] IBU standard dose 30.88 [a]	IBU high dose 1300.2 [a] IBU standard dose 1324.3 [a]	NR	Probably Low	Echo confirmed hs-PDA; criteria not specified	Oral high dose Ibuprofen at 15 mg/kg followed by two 7.5 mg/kg doses at 24h interval	Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h
55	Gersony 1983	English	405	NR	NR	NR	Low	Clinical signs of hs-PDA & LA:AO>1.15 on echocardiography	IV Indomethacin 3 doses; 1st 0.2mg/kg; Infants less than 48 hours of age at the time of trial entry received 0.1 mg/kg body weight for the second and third doses of the drug. Infants who were 2-7 days of age at the time of the first dose received 0.2 mg/kg for the second and third doses, and those infants 8 days or older received 0.25 mg/kg body weight for their second and third doses	Placebo (IV colorless solution)
56	Ghanem 2010	English	66	IBU 28.8 [a] (2.8) [c] PLAC 28.9 [a] (2.7) [c]	IBU 1035 [a] (353) [c] PLAC 1047 [a] (403) [c]	NR	Probably High	LA:AO >1.4 or PDA >1.5 mm	Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h	Placebo
57	Gimeno Navarro 2005	Spanish	47	INDO 28.5 [b] (27-30) [d] IBU 28 [b] (24-31) [d]	INDO 1205.8 [a] (512.9) [c] IBU 1169 [a] (489.5) [c]	NR	Probably Low	PDA/Pulmonary root ratio >0.3; Diastolic reverse flow in the abdominal aorta	IV Indomethacin 0.2 mgkg every 12 h x 3doses	IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h
58	Gokmen 2011	English	102	IBU oral 28.5 [a] (1.9) [c] IBU IV 28.7 [a] (2.1) [c]	IBU oral 1170 [a] (297) [c] IBU IV 1205 [a] (366) [c]	NR	Low	PDA >1.5 mm; LA:AO >1.5; Left-to-right shunting of blood across PDA; End-diastolic reversal of blood flow in the aorta or poor cardiac function	IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h	Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h

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Ref No	Author & year of publication	Language of publication	# of infants enrolled	Gestational age at birth (in weeks) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])]	Birth weight (in grams) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])]	Age at start of treatment (days) [Mean [a] (SD [c]]/ [Median [b] (IQR [d]/ Range [e])]	Overall assessment of risk of bias	Criteria for diagnosis of hs-PDA	Intervention characteristics (drug: route & dose)	
59	Hammerman 1990	English	39	INDO 28 [a] (3) [c] PLAC 27 [a] (7) [c]	INDO 1099 [a] (435) [c] PLAC 1040 [a] (394) [c]	INDO 9 [a] (4) [c] PLAC 10 [a] (5) [c]	Probably Low	The presence of an infraclavicular and precordial systolic murmur consistent with PDA, plus any two of the following: bounding pulse rate, diastolic pressure of ≤25 mm Hg, and pulmonary plethora or cardiomegaly on chest radiographs. The clinical diagnosis was confirmed by pulsed Doppler echocardiography; echo criteria not specified	IV Indomethacin (3 initial doses, 0.2 mg/kg/dose every 12 hours followed by 5 more doses 0.2 mg/kg/dose every 24 hours)	Placebo (IV saline)
60	Hammerman 1995	English	18	INDO bolus 29 [a] (2) [c] INDO continuous 28 [a] (2) [c]	INDO bolus 1200 [a] (0.3) [c] INDO continuous 1100 [a] (0.2) [c]	NR	Probably Low	Measurements of maximal systolic pressure gradient and % filling of the pulmonary artery were recorded as reflections of severity of ductal shunting	IV Indomethacin 0.2 mg/kg by a 1-minute rapid injection for the first dose and then 0.1 mg/kg again by rapid injection, every 12 hours for two additional doses (total indomethacin dose 400 mcg/kg)	IV Indomethacin infusion at 11 mcg/kg/hour to run for 36 hours (total dose 396 mcg/kg)
61	Hammerman 2008	English	63	INDO continuous 27.8 [a] (2.8) [c] IBU IV 27.8 [a] (2.6) [c]	INDO continuous 1100 [a] (0.45) [c] IBU IV 1060 [a] (0.35) [c]	INDO continuous 4.5 [b] (2.3-7.7) [d] IBU IV 3.7 [b] (2.5-5.5) [d]	Low	Left to right PDA shunting on Doppler echo	IV Indomethacin infused continuously for 36 h at a rate of 17 mcg/kg/h	IV Ibuprofen initial dose of 10 mg/kg followed by two doses of 5 mg/kg at 24-h intervals
62	Jegatheesan 2008	English	105	INDO low dose 25.8 [a] (1.2) [c] INDO high dose 25.5 [a] (1.2) [c]	INDO low dose 816 [a] (177) [c] INDO high dose 791 [a] (158) [c]	NR	Probably High	Hs-PDA on echo; criteria not specified	IV Indomethacin 0.1mg/Kg/d x 3d	IV Indomethacin 0.2-0.5mg/Kg/d x3d
63	Kluckow 2014	English	92	INDO 26 [a] (1.4) [c] PLAC 26 [a] (1.4) [c]	INDO 892 [a] (205) [c] PLAC 876 [a] (203) [c]	INDO 0.34 [a] (0.12) [c] PLAC 0.37 [a] (0.14) [c]	Low	The PDA diameters used were >1.8 mm at postnatal age 3–5 h, >1.6 mm at post- natal age 6–8 h and >1.3 mm at postnatal age 9–12h	IV Indomethacin 0.2 mg/kg followed by 0.1 mg/kg	Placebo
64	Krauss 1989	English	27	NR	INDO 1183 [a] (266) [c] No treatment 1022 [a] (224) [c]	NR	Probably High	Clinical signs of PDA along with PDA diameter and LA:AO ratio on echocardiography; criteria not specified	3 doses of IV Indomethacin 0.2 mg/kg/dose between 72-96 h of age	No treatment
65	Lago 2002	English	175	INDO 29 [a] (3) [c] IBU 28 [a] (2) [c]	INDO 1214 [a] (427) [c] IBU 1126 [a] (412) [c]	NR	Probably High	Typical PDA flow pattern obtained by colour Doppler echocardiography. Shunting was defined as haemodynamically significant if a disturbed diastolic flow was easily detectable in the main pulmonary artery with a diastolic backflow in the aorta immediately below the ductus arteriosus and a forward flow above the ductal insertion	IV Indomethacin 3 doses of 0.2 mg/kg at 12 h intervals	IV Ibuprofen initial dose of 10 mg/kg followed by two doses of 5 mg/kg each after 24 and 48h
66	Lago 2014	English	111	INDO bolus 27.4 [a] (2.7) [c] INDO continuous 27.3 [a] (2.1) [c]	INDO bolus 1027.1 [a] (346.1) [c] INDO continuous 1012.1 [a] (315.4) [c]	INDO bolus 3.3 [a] (1) [c] INDO continuous 2.7 [a] (0.7) [c]	Low	Shunting was hemodynamically significant if 2 or more of the following conditions were met: (1) transductal PDA diameter > 1.4 mm/kg; (2) unrestrictive pulsatile transductal flow [PDA maximum velocity (Vmax) <2.0 m/s]; (3) mild-to-moderate left heart volume loading [LA/Ao ratio >1.4]; (4) increased pulmonary perfusion, i.e. mean and end-diastolic flow velocity in the left pulmonary artery ≥0.42 and ≥0.20 m/s, respectively, and (5) increased left ventricular output and consistent peripheral hypoperfusion in the superior vena cava, i.e. left ventricular output/superior vena cava (LVO/SVC) flow ratio ≥4	IV Ibuprofen bolus (Daily continuous infusions of 5% dextrose and IBU boluses of 10, 5 and 5 mg/kg administered over 15 min, 24h apart)	IV Ibuprofen continuous infusions of 10mg/kg (0.416 mg/kg/h), 5 mg/kg (0.208 mg/kg/h) and 5 mg/kg(0.208 mg/kg/h), and boluses of equal volumes of 5% dextrose administered over 15 min, 24 h apart
67	Lee 2003	English	140	27.4 [a] (2.7) [c]	955 [a] (264) [c]	2.2 [b] (1.58-3.08) [d]	Low	Clinical criteria (murmur, hyperactice precordium, hypotension, apnea, high FiO_2 along with PDA: >1.5mm on echo	IV Indomethacin 0.1mg/Kg every 12h x 3doses infused over 30 mins	IV Indomethacin 0.1 mg/kg every 24 h x 6 doses infused over 30 min
68	Lee 2008	Korean	34	INDO 29.4 [a] (2.6) [c] IBU 30.2 [a] (3.0) [c]	INDO 1290 [a] (360) [c] IBU 1480 [a] (560) [c]	INDO 3.9 [a] (1.8) [c] IBU 3.9 [a] (1.4) [c]	Probably Low	PDA >1.5mm; LA:AO >1.3	IV Indomethacin 0.2 mgkg every 12 h x 3doses	Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h

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69	Lin 2017	English	144	INDO 26.3 [a] (1.6) [c] IBU 26.2 [a] (1.7) [c]	INDO 812 [a] (160) [c] IBU 801 [a] (156) [c]	INDO 3.3 [a] (1.4) [c] IBU 3.2 [a] (2) [c]	Low	Cardiovascular dysfunction score>3 & LA:Ao > 1.3	IV Indomethacin 0.2 mg/kg followed by 0.1 mg/kg q 24h x 2 doses	IV Ibuprofen: Initial dose of 10 mg/kg, followed by two doses of 5 mg/kg each at 24h interval
70	Lin 2012	Chinese	64	IBU 31.2 [a] (2.4) [c] PLAC 30.8 [a] (2.3) [c]	IBU 1301 [a] (260) [c] PLAC 1350 [a] (221) [c]	IBU 23 [a] (4) [c] PLAC 20 [a] (5) [c]	Probably Low	Clinical signs of hs-PDA along with following echo criteria: PDA ≥1.5mm & Left-right PDA shunt	Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h	Placebo (Oral saline)
71	Merrit 1981	English	24	NR	NR NR	NR	High	Clinical signs of hs-PDA along with LA:AO >1.2 on echo	IV Indomethacin 0.2 mg/kg every 24h x 3days	No treatment
72	Monset-Couchard 1983	French	24	INDO 30.6 [a] (NR) No treatment 30.6 [a] (NR)	INDO 1434 [a] (361) [c] No treatment 1398 [a] (471)	NR	High	Clinical signs of hs-PDA & increased LA:AO on echo	IV Indomethacin 0.2 mg/kg single dose	No treatment
73	Mosca 1997	English	16	INDO 28 [b] (25-30) [e] IBU 29 [b] (27-31) [e]	INDO 820 [b] (600-1390) [e] IBU 855 [b] (620-1620) [e]	NR	Probably High	Mechanically ventilated for RDS & LA:AO >1.4 on echo	IV Indomethacin 0.2 mg/kg every 24h x 3days	IV Ibuprofen 10mg/kg every 24h x 3days
74	Mullett 1982	English	47	PLAC 29.5 [a] (NR) INDO 30.1 [a] (NR)	PLAC 1212 [a] (NR) INDO 1237 [a] (NR)	PLAC 7.5 [a] INDO 7.4 [a]	Probably Low	Enrolment criterion: Heart murmur consistent with PDA PDA closure criteria: complete cessation of the PDA murmur or a decrease in intensity by II of VI grades, resting heart rate of less than 145 beats per minute, improvement in respiratory status (removal from assistance or 30% decrease in Fi02), and LA/AO ratio of > 1.2:1 on echo	Oral Indomethacin 0.2 mg/kg every 24h x 2days	Placebo (Oral cornstarch)
75	Nestrud 1980	English	23	INDO 30.8 [a] (1.8) [c] PLAC 28.1 [a] (2.0) [c]	INDO 1287 [a] (325) [c] PLAC 1189 [a] (376) [c]	INDO 20.1 [a] (16.7) [c] PLAC 14.4 [a] (10) [c]	Low	Presence of a large left-right shunt on echo; LA:AO<1.3 did not exclude patient from the study if there was overwhelming clinical signs of congestive cardiac failure	Oral Indomethacin 0.2 mg/kg every 12h x 3 doses	Placebo (Oral saline)
76	Neu 1981	English	21	29.3 [a] (0.6) [c]	1142 [a] (80) [c]	NR	Low	Clinical signs of hs-PDA and increased LA:AO ratio on echo; cut-off not specified	Oral Indomethacin 0.25mg/kg every 24h x 2doses	Placebo
77	Oncel 2014	English	80	IBU 27.3 [a] (2.1) [c] PARA 27.3 [a] (1.7) [c]	IBU 973 [a] (224) [c] PARA 931 [a] (217) [c]	NR	Probably Low	PDA >1.5 mm, LA:AO >1.5, end diastolic reversal of blood flow in the aorta, or poor cardiac function in addition to clinical signs of PDA.	Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h	Oral acetaminophen 15 mg/kg every 6 h for 3 days
78	Osborn 2003	English	70	PLAC 26.9 [a] (1.8) [c] INDO 26.7 [a] (1.6) [c]	PLAC 1002 [a] (288) [c] INDO 958 [a] (237.2) [c]	4.3 [b] (2-12) [e]	Probably Low	PDA>1.6mm	IV Indomethacin 0.2mg/kg single dose	Placebo
79	Patel 2000	English	33	INDO 26.7 [b] (23.2-30) [e] IBU 26.0 [b] (23.9-35.0) [e]	INDO 838 [b] (458-1377) [e] IBU 790 [b] (620-2780) [e]	INDO 7 [b] (3-21) [e] IBU 8 [b] (3-20) [e]	Probably Low	Clinical signs of hs-PDA & left-right PDA shunt on echo	IV Indomethacin 0.2 mg/kg every 12 h x 3doses	IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h
80	Pezzati 1999	English	17	INDO 29.5 [a] (2.6) [c] IBU 29.1 [a] (2.1) [c]	INDO 1277 [a] (440) [c] IBU 1151 [a] (426) [c]	INDO 1.38 [a] (0.22) [c] IBU 1.33 [a] (0.18) [c]	Probably High	LA:AO>1.4	IV Indomethacin 0.2 mg/kg followed by two doses of 0.1mg/kg every 24 hours	IV Ibuprofen 10 mg/kg followed by 5 mg/kg at 24 and 48 h
81	Pistulli 2014	English	68	NR	NR	NR	Probably High	PDA >1.5 mm, LA:AO >1.4, and a left-to-right shunting of blood in addition to clinical signs of hs-PDA.	IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h	IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h
82	Pourarian 2008	English	20	INDO 33.2 [a] (3.1) [c] IBU 31.3 [a] (4.4) [c]	INDO 1720 [a] (6302) [c] IBU 1860 [a] (402) [c]	INDO 6.4 [a] IBU 5.5 [a]	Probably Low	Presence of hs-PDA on echo; criteria not specified	Oral Indomethacin 0.2 mg/kg every 24h x 3days (Administration of 2nd and 3rd doses was dependent on achievement of ductal closure after the initial dose)	Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg after 24 and 48 h

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83	Pourarian 2015	English	30	IBU high dose 2.6 [a] (30) [c] IBU standard dose 2.1 [a] (31.4) [c]	IBU high dose 1339 [a] (542) [c] IBU standard dose 1493 [a] (346) [c]	NR	Probably Low	Presence of hs-PDA on echo; criteria not specified	Oral high dose Ibuprofen at 20 mg/kg followed by two 10 mg/kg doses at 24h interval	Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h
84	Rennie 1991	English	121	INDOIVPROLONGED 27 [a] (2.2) [c] INDOIV 27 [a] (2.2) [c]	INDOIVPROLONGED 1116 [a] (340) [c] INDOIV 1135 [a] (340) [c]	NR	Probably High	Clinical signs of hs-PDA	IV Indomethacin 0.1mg/kg every 24 hours x 6days	IV Indomethacin 0.2 mg/kg every 12 h x 3 doses
85	Rhodes 1988	English	70	INDOIVPROLONGED 27 [a] (2.3) [c] INDOIV 27 [a] (2.2) [c]	INDOIVPROLONGED 975 [a] (234) [c] INDOIV 972 [a] (245) [c]	<1	Probably High	Left-to-right shunting through PDA on echo	IV Indomethacin initial two doses of 0.15 mg/kg given 12h apart followed by 0.1 mg/kg every day for 5 days	IV Indomethacin two doses of 0.15 mg/kg given 12h apart
86	Romagnoli 1997	English	34	INDOIVFRU 27.9 [a] (2.0) [c] INDOIV 28.9 [a] (1.9) [c]	INDOIVFRU 1088 [a] (300) [c] INDOIV 1159 [a] (238) [c]	INDOIVFRU 3.0 [a] (1.7) [c] INDOIV 3.9 [a] (3.4) [c]	Probably High	Clinical criteria: appearance of systolic or continuous murmur, respiratory "step-up" with increased ventilatory pattern, progressive increase of basal heart rate, and presence of bounding radial pulses. The clinical diagnosis was confirmed by color Doppler echocardiography.	IV Indomethacin 0.2 mg/kg every 12 h x 3doses PLUS IV Frusemide 0.1mg/kg every 12h x 3 doses	IV Indomethacin 0.2 mg/kg every 12 h x 3doses
87	Rudd 1983	English	30	PLAC 29.0 [a] (1.7) [c] INDO 28.9 [a] (1.2) [c]	PLAC 1170 [a] (211) [c] INDO 1105 [a] (251) [c]	PLAC 10.2 [a] (5.3) [c] INDO 11.0 [a] (8.1) [c]	Probably Low	LA:AO Ratio ≥ 1.2	Oral Indomethacin 0.2 mg/kg every 12h x 3 doses (maximum)	Placebo
88	Sangtawesin 2008	English	62	IBU 29.3 [a] (1.94) [c] PLAC 29.3 [a] (2.16) [c]	IBU 1156.9 [a] (263.6) [c] PLAC 1162.9 [a] (261.0) [c]	IBU 0.75 [a] (0.25) [c] PLAC 0.84 [a] (0.24) [c]	Probably Low	PDA> 1.5mm LA:AO>1.4	Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h	Placebo (oral orange starch)
89	Sosenko 2012	English	105	IBU 26 [b] (23-28) [d] PLAC 25 [b] (24-29) [d]	IBU 854 [a] (204) [c] PLAC 842 [a] (203) [c]	3	Low	Presence of PDA with either predominantly left-to-right or bidirectional shunt	IV Ibuprofen initial dose of 10 mg/kg followed by two doses of 5 mg/kg each after 24 and 48 h	Placebo (5% Dextrose IV)
90	Su BH 1999	English	93	INDO 27.8 [a] (2.5) [c] INDOIVECHOGUIDED 27.2 [a] (2.6) [c]	INDO 1039 [a] (244) [c] INDOIVECHOGUIDED 955 [a] (271)	NR	Probably High	Pulsatile or growing pattern of left-right PDA shunt on Doppler echo	IV Indomethacin 0.2 mg/kg for the first dose, then 0.1 mg/kg in infants less than 48 hours old, 0.2 mg/kg in infants over 48 hours, every 12 hours for another two doses	IV Indomethacin: one unique dose of 0.2 mg/kg initially followed by subsequent doses as per the standard IV Indomethacin regimen only if echocardiography shows hs-PDA
91	Su BH 2008	English	119	IBU 25 [b] (23-28) [d] INDO 25 [b] (23-28) [d]	IBU 825 [b] (550-990) [d] INDO 762 [b] (540-980) [d]	IBU 0.33 [b] (0.17-0.88) [d] INDO 0.33 [b] (0.12-1.0) [d]	Probably Low	Pulsatile or growing pattern of left-right PDA shunt on Doppler echo	IV Indomethacin 0.2mg/kg as the initial dose followed by 0.1 mg/ kg in infants less than 48 hours old, 0.2 mg/kg in infants over 48 hours at 24-hour intervals as indicated by PDA flow pattern	IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h as indicated by the PDA flow pattern
92	Su PH 2003	English	63	IBU 28.7 [a] (2.2) [c] INDO 28.2 [a] (2.4) [c]	IBU 1133.9 [a] (200.0) [c] INDO 1109.5 [a] (244.1) [c]	IBU 4.1 [a] (1.3) [c] INDO 4.9 [a] (3.7) [c]	Probably High	Left-right PDA shunt; LA:AO> 1:3; PDA>1.5 mm.	IV Indomethacin 0.2 mgkg every 12 h x 3doses	IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h

eTable 4. Clinical & Methodological Characteristics of Included Studies (cont'd….)

Ref No	Author & year of publication	Language of publication	# of infants enrolled	Gestational age at birth (in weeks) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])]	Birth weight (in grams) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])]	Age at start of treatment (days) [Mean [a] (SD [c])]/ [Median [b] (IQR [d]/ Range [e])]	Overall assessment of risk of bias	Criteria for diagnosis of hs-PDA	Intervention characteristics (drug: route & dose)	
93	Supapannachart 2002	English	18	IBU 30.1 [a] (2.7) [c] INDO 30.4 [a] (2.6) [c]	IBU 1446.7 [a] (38.5) [c] INDO 1431.7 [a] (1431.7) [c]	IBU 3.0 [a] (1.1) [c] INDO 3.4 [a] (2.2) [c]	High	Clinical Criteria: (a) Systolic murmur at left upper parasternal border; (b) Continuous murmur at left upper parasternal border; (c) Active precordium; (d) Bounding pulse, wide pulse pressure (pulse pressure >35 mmHg) (e) Tachycardia (heart rate >170/min) (f)Hepatomegaly (g) Chest X-ray with cardiomegaly (CT ratio>0.6) or increased pulmonary vasculature. Any infant with more than 3 of the above criteria was diagnosed with symptomatic PDA.	IV Indomethacin 0.2 mgkg every 12 h x 3doses	Oral Ibuprofen 10mg/kg daily for 3 consecutive days
94	Tammela 1999	English	61	INDOIV 27.9 [a] (2.3) [c] INDOIVPROLONGED 27.3 [a] (1.94) [c]	INDOIV 1154 [a] (388) [c] INDOIVPROLONGED 2094 [a] (298) [c]	INDOIV 4.3 [a] (4.4) [c] INDOIVPROLONGED 3.1 [a] (1.7) [c]	Probably High	Clinical signs & left-right PDA shunt on Doppler echo	IV Indomethacin 0.2 mg/kg followed by 2 doses of 0.1 mg/kg at 12-hour intervals	IV Indomethacin: 7 doses of 0.1mg/kg at 24 h intervals
95	Van Overmeire 1995	English	75	INDO 29.6 [a] (2.5) [c] ASA 29.7 [a] (2.5) [c]	INDO 1292 [a] (434) [c] ASA 1298 [a] (494) [c]	INDO 3.45 [a] (0.69) [c] ASA 3.43 [a] (0.65) [c]	Probably High	1) Moderate PDA: Disturbed diastolic flow easily detectable at all sites of the pulmonary trunk, a diastolic back flow was present in the aorta immediately beneath the PDA and a forward flow above the PDA; 2) Large (severe) PDA: If a diastolic back flow was detectable in the abdominal aorta at the level of the celiac arterial trunk and if dilatation of the left atrium was present expressed as a LA:AO> 1.7	IV Indomethacin 0.2 mg/kg every 12 h x 3doses	IV Aspirin 15mg/kg/dose every 6h x 4doses
96	Van Overmeire 1997	English	40	INDO 28.7 [a] (1.9) [c] IBU 29.0 [a] (2.4) [c]	INDO 1210 [a] (360) [c] IBU 1270 [a] (450)	INDO 3.1 [a] (0.5) [c] IBU 3.2 [a] (0.4) [c]	Probably Low	(1) Moderate PDA shunt: if a disturbed diastolic flow was easily detectable at all sites of the pulmonary trunk, a diastolic back flow was present in the aorta immediately beneath the PDA and a forward flow above the PDA; (2) Severe PDA shunt: If a diastolic back flow was detectable in the aorta and if dilatation of the left atrium was present and expressed as a LA:AO>1.6	IV Indomethacin 0.2 mg/kg every 12 h x 3doses	IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h
97	Van Overmeire 2000	English	148	INDO 29.0 [a] (2.1) [c] IBU 29.0 [a] (2.3) [c]	INDO 1230 [a] (380) [c] IBU 1230 [a] (390) [c]	INDO 3.1 [a] (0.5) [c] IBU 3.1 [a] (0.6) [c]	Probably Low	(1) Moderate PDA shunt: If a disturbed diastolic flow was easily detected in the main pulmonary artery with a diastolic reversed flow in the aorta beneath the ductus and a forward flow above the ductal insertion; (2) Severe PDA shunt: If a diastolic backflow in the aorta was straightforward and if dilatation of the left atrium was present (LA:AO > 1.6)	IV Indomethacin 0.2 mgkg every 12 h x 3 doses	IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h
98	Van Overmeire 2001	English	127	INDO 28.9 [a] (2.0) [c] INDOLATE 29.2 [a] (2.1) [c]	INDO 1210 [a] (370) [c] INDOLATE 1270 [a] (365) [c]	NR	Probably Low	(1) Moderate PDA shunt: If a disturbed diastolic flow was easily detected in the main pulmonary artery with a diastolic reversed flow in the aorta beneath the ductus and a forward flow above the ductal insertion; (2) Severe PDA shunt: If a diastolic backflow in the aorta was straightforward and if dilatation of the left atrium was present (LA:AO > 1.5).	IV Indomethacin 0.2 mgkg every 12 h x 3doses started on day 3	IV Indomethacin 0.2 mgkg every 12 h x 3doses started on day 7
99	Yadav 2014	English	83	IBU 29.65 [a] (3.15) [c] INDO 30.29 [a] (3.14) [c]	IBU 1440 [a] (450) [c] INDO 1380 [a] (450) [c]	IBU 10.1 [a] (6.1) [c] INDO 9.8 [a] (6.0) [c]	Probably Low	PDA> 1.5mm LA:AO>1.4	Oral Indomethacin three doses (0.20–0.25 mg/kg every 24 h) depending on the gestational age (initial dose was 0.2 mg/kg, subsequent doses 2–7 days of age were 0.2mg/kg/dose every 24 h for two doses; >7 days of age 0.25mg/kg/dose every 24 h for two doses)	Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h

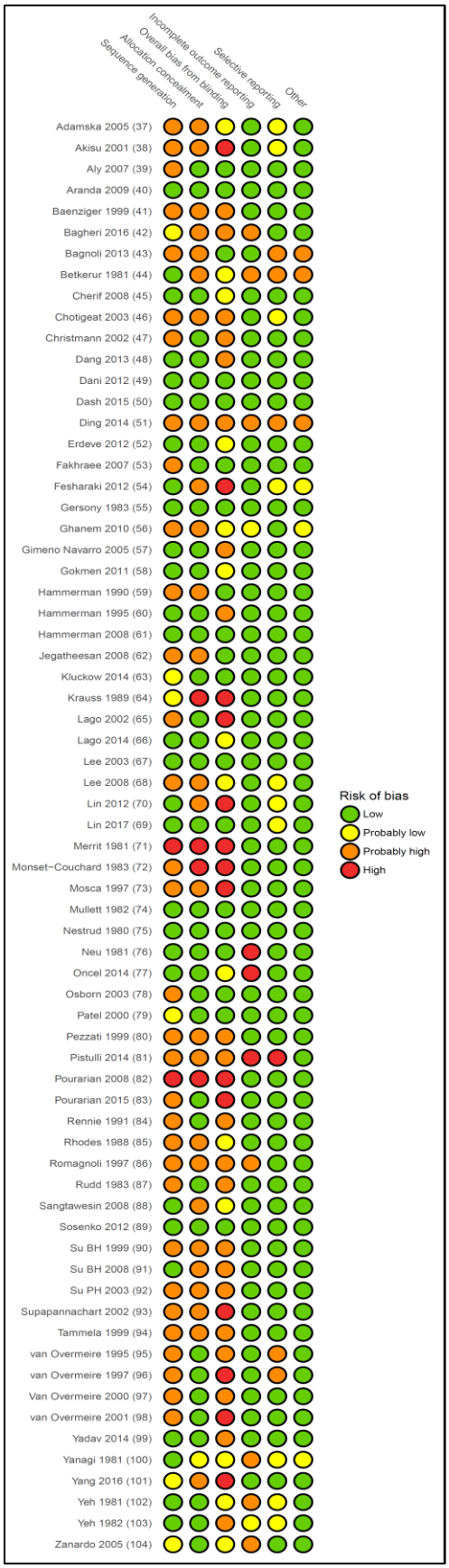
eTable 4. Clinical & Methodological Characteristics of Included Studies (cont'd….)

Ref No	Author & year of publication	Language of publication	# of infants enrolled	Gestational age at birth (in weeks) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])]	Birth weight (in grams) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])]	Age at start of treatment (days) [Mean [a] (SD [c])]/ [Median [b] (IQR [d]/ Range [e])]	Overall assessment of risk of bias	Criteria for diagnosis of hs-PDA	Intervention characteristics (drug: route & dose)	
100	Yanagi 1981	English	43	PLAC 30.4 [a] (1.0) [c] INDO 29.4 [a] (1.0) [c]	PLAC 1500 [a] (200) [c] INDO 1200 [a] (100) [c]	PLAC 9.1 [a] (6.6) [c] INDO 8.6 [a] (9.8) [c]	Probably Low	LA:AO ≥1.3 and continuous requirement of ventilator support	Oral Indomethacin was administered in 2 phases: In phase 1, 2 mg/kg of indomethacin was administered as the first dose, second and third doses were administered 24 and 48 hours following the first dose as long as the clinical and echocardiographic criteria of sPDA persisted. In phase 2, the dose interval was decreased to eight rather than 24 hours and the second and third doses were thus administered at eight and 16 hours after the first dose. Digitalis and furosemide were used as cointerventions	Oral placebo was used. Small amount of cornstarch was added to 250 mg of lactose to achieve an appearance similar to that of the indomethacin vials. Just prior to administration, 9.5 ml of normal saline was added to each vial and 0.4 ml/kg of this suspension (0.2 mg/kg of indomethacin or placebo) was administered
101	Yang 2016	English	87	IBU 33.4 [a] (2.1) [c] PARA 33.6 [a] (2.1) [c]	IBU 2091 [a] (657) [c] PARA 2219 [a] (606) [c]	IBU 5.8 [a] (2) [c] PARA 6.4 [a] (1.8) [c]	Probably High	PDA > 1.4 mm; LA:AO>1.4	Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h	Oral acetaminophen 15 mg/kg every 6 h for 5 days
102	Yeh 1981	English	55	PLAC 30.2 [a] (2.3) [c] INDO 31.5 [a] (2.3) [c]	PLAC 1167 [a] (354) [c] INDO 1233 [a] (408) [c]	PLAC 10.9 [a] (6.1) [c] INDO 8.9 [a] (5.3) [c]	Low	Cardiovascular dysfunction score ≥ 3 or LA:AO ≥ 1.3 on echo	IV Indomethacin: One dose of 0.3 mg/kg was administered intravenously and was repeated at intervals of about 24 hours up to a maximum of three doses, unless the PDA murmur disappeared. IV Frusemide (1mg/kg) and fluid restriction were used as cointerventions in both groups	IV Placebo: Identical syringes containing either indomethacin 1 mg in 1 ml saline diluent or a placebo consisting of 1 ml of saline only were prepared. A dose of 0.3 ml/kg was administered intravenously and was repeated at intervals of about 24 hours up to a maximum of three doses, unless the PDA murmur disappeared.
103	Yeh 1982	English	19	INDO 30.4 [a] (0.9) [c] INDOIVFRU 30.7 [a] (0.8) [c]	INDO 1120 [a] (390) [c] INDOIVFRU 1190 [a] (100) [c]	INDO 10.7 [a] (3.4) [c] INDOIVFRU 9.5 [a] (1.7) [c]	Probably Low	Clinical criteria: (1) evidence of PDA, and (2) evidence of significant clinical cardiovascular Dysfunction along with echocardiographic left atrium/aortic root dimension ratio (LA:AO) ≥ 1.30	IV Indomethacin 0.3mg/kg every 24h up to 3 doses	IV Indomethacin 0.3mg/kg followed immediately IV Frusemide (1mg/kg) every 24h up to 3 doses
104	Zanardo 2005	English	46	IBU 26 [b] (23-34) [e] INDO 27.5 [b] (23-33) [e]	IBU 857.5 [b] (500-2110) [e] INDO 977.5 [b] (616-2450) [e]	IBU 3 [b] (2-17) [e] INDO 2.5 [b] (2-12) [e]	Probably Low	Infants with RDS who required ventilator support along with typical flow pattern of hs-PDA on Doppler echo	IV Indomethacin 0.2 mg/kg every 12 h x 3doses	IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h

Abbreviations:

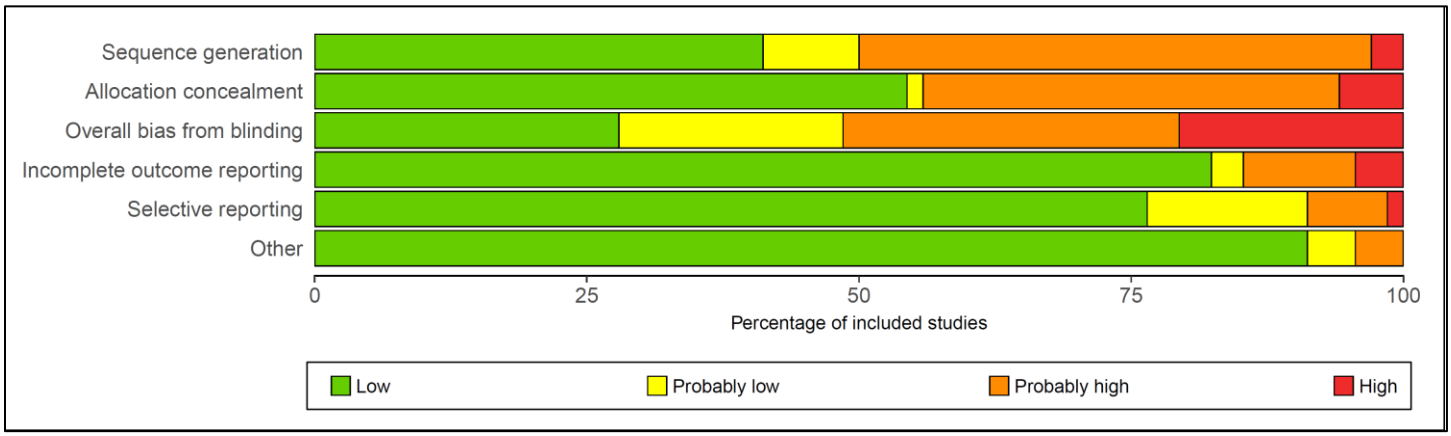
- SD: Standard deviation
- IQR: Interquartile range
- INDO: Indomethacin
- IBU: Ibuprofen
- PLAC: Placebo
- PARA: Acetaminophen
- NR: Not reported
- ASA: Acetylsalicylic acid (aspirin)
- INDOLATE: Intravenous indomethacin standard dose; late initiation of therapy (started on or beyond day 7)
- INDOIVPROLONGED: Intravenous indomethacin prolonged treatment course
- INDOIVFRU: Intravenous indomethacin standard dose along with Frusemide
- INDOIVECHOGUIDED: Intravenous indomethacin standard dose; duration guided by echo assessment of PDA
- hs-PDA: hemodynamically significant patent ductus arteriosus
- LA:AO: Left atrium to aortic root ratio on echocardiography
- LV:AO: Left ventricle to aortic root ratio on echocardiography

eFigure 2. Detailed risk of Bias assessment of individual studies



- ***Risk of Bias (RoB) assessment items:*** Sequence generation; Allocation concealment; Blinding; Incomplete outcome data; Selective reporting of outcomes; other biases
- ***RoB categories:*** Low; Probably low; Probably High; High

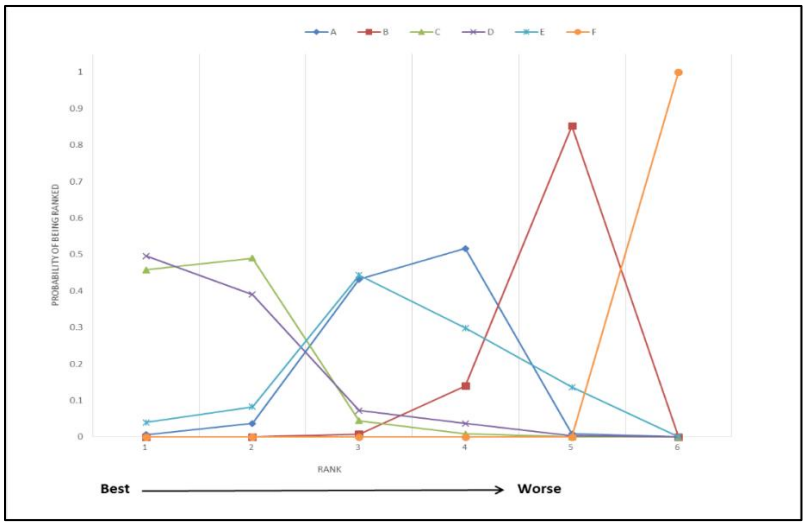
eFigure 3. Assessment summary across the risk of bias items



- ***Risk of Bias (RoB) assessment items:*** Sequence generation; Allocation concealment; Blinding; Incomplete outcome data; Selective reporting of outcomes; other biases
- ***RoB categories:*** Low; Probably low; Probably High; High
- ***Number of studies included in the summary:*** 68

eText 2. Guide to interpreting NMA results (rankograms; SUCRA; Network GRADE)

eText 2(a). Rankograms examples and interpretation



eText 2(a):rankogram example figure

The figure above displays an example of a rankogram in a hypothetical study comparing 6 interventions for a specific outcome. The figure shows each intervention with a different color and symbol. The horizontal axis displays the ranking from 1 to 6. Ranking should be interpreted from best (rank 1), to worst (rank 6), for this specific outcome. The vertical axis displays the probability of being ranked in any specific ranking position, from 0 to 1. In order to systematically interpret a rankogram, one should start by focusing on rank 1 first, establish which intervention might be the best and then follow the same for each rank. As shown in the figure above, in rank 1, the treatment D showed slightly more than 0.5 probability of being ranked the best, or being ranked in the first position. After treatment D, treatment C had a probability of approximately 0.46 of being ranked in the first place, while treatment E had a probability of approximately 0.05 of being ranked the first. Of note, treatments A, B and F only had probabilities of around 0 of being best ranked. Similarly, the last position on the right of the curve, rank 6, shows the probability of being ranked as the worst treatment. In this case, intervention F had the highest probability of being in rank 6 (approximately 0.99).

In summary, rankograms allow the reader to see for each treatment, the probability of being ranked in the first, second, third position, and so on, until the worst (depending on the number of interventions analyzed) (3). In this case, treatment D was found to be the one with the highest probability of being the best while treatment F had the highest probability of being the worst treatment.

eText 2(b). SUCRA examples and interpretation

Surface under the cumulative ranking curve (SUCRA) summarizes the information from the rankograms as a single number. Its calculation is based on the cumulative probabilities of the treatments being ranked in each position, and the SUCRA is the final area under the curve of the graph for these probabilities. This is a simple numerical summary to supplement the graphical display. SUCRA would be 1 when a treatment is certain to be the best and 0 when a treatment is certain to be the worst (4). If a treatment always ranks first, then SUCRA=1, and if it always ranks last, it will have SUCRA=0. For example, if cumulative probabilities are computed using the information from the rankogram above, we would obtain the mean SUCRA value for each intervention, as presented in the SUCRA example table below. The median ranks for each treatment option are also provided along with. This enables overall ranking of the treatments based on the mean SUCRA value. In this case, treatment C emerges as the best (SUCRA, 0.88), followed by D, E, A, B and lastly F (SUCRA, 0). Thus, SUCRA simplifies the information on the ranking distribution of each treatment into a single number, which helps to summarize the ranking statistics in a complex network meta-analysis.

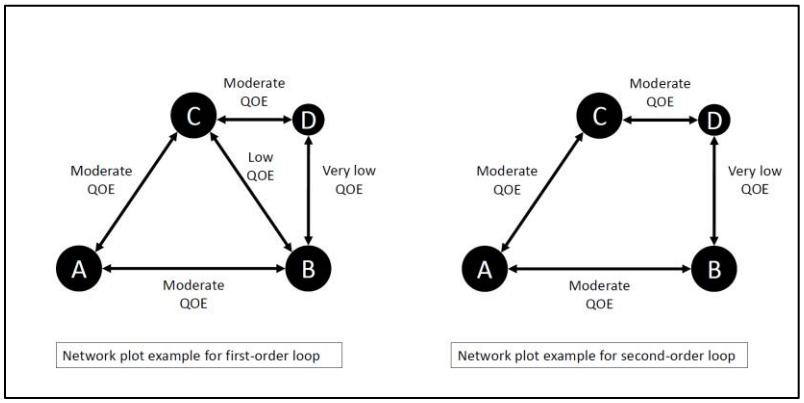
eText 2(b):SUCRA example table

Treatment	Mean SUCRA (standard deviation)	Median rank (95% credible intervals)
A	0.50 (0.12)	4 (2-4)
B	0.23 (0.08)	5 (4-5)
C	0.88 (0.12)	2 (1-3)
D	0.87 (0.16)	2 (1-4)
E	0.52 (0.19)	3 (1-5)
F	0	6 (6-6)

eText 2(c). Network GRADE Assessment Strategy

The assessment of the confidence in the estimates (quality of evidence) for each reported outcome was performed according to the GRADE approach (5). To assess GRADE quality of evidence in a network meta-analysis, both direct and indirect comparisons are taken into account. A ***direct comparison*** between two treatment options is defined as a comparison based on head-to-head RCTs between the two treatment options. An ***indirect comparison*** between two treatment options is computed when no head-to-head RCTs have been conducted between the two respective treatment options (described in detail below). Initially, direct comparisons were assessed and rated based on the following categories: risk of bias; indirectness; inconsistency (which is determined based on the heterogeneity); imprecision and publication bias (6-9). This was followed by assessment of confidence from indirect estimates and the final step was assessment of confidence in the NMA estimates (10). The final confidence was rated based on four levels: high, moderate, low and very low.

For rating confidence in the indirect comparisons, information obtained from the first and second order loops in the network was used as shown in the example figure below.

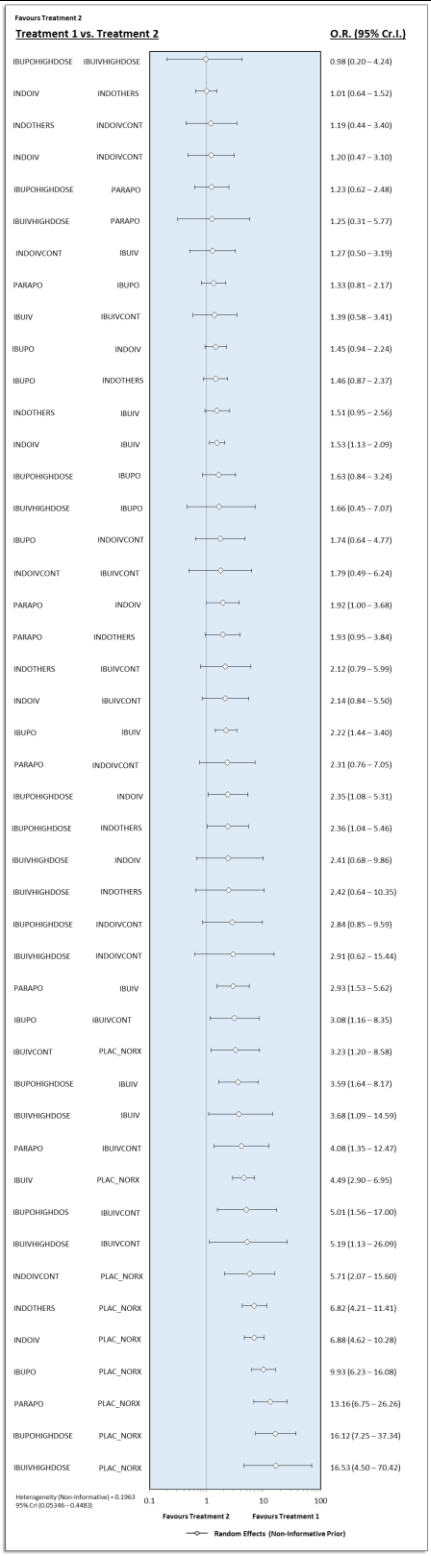


In the above networks, each node indicates a treatment strategy and each of two-way arrows indicates a direct comparison between two strategies. In the first figure above *(network plot example for first-order loop)*, for the comparison of A vs. B, the pathway of A-C-B is a first-order loop and the pathway of A-C-D-B is a second-order loop. The quality of evidence of indirect comparisons was derived from the quality of evidence of the first order loops. The quality of evidence of a first-order loop was derived from the lowest quality of evidence among direct comparisons within the first-order loop. In the first example figure, the quality of evidence of the indirect comparison of A vs. B was the lower quality of evidence among 2 direct comparisons of A vs. C (moderate) and B vs. C (low), which was low quality of evidence. When an indirect comparison had two or more first-order loops, the highest quality of evidence among its first-order loops were used for the quality of evidence of the indirect comparison. For example, the quality of evidence for the indirect comparison of B vs. C was the highest quality of evidence of the 2 first order loops of B-A-C (moderate) and B-D-C (very low), which was moderate quality of evidence. When no first order loop was available, the quality of evidence for an indirect comparison was derived from the second-order loops. In the second figure above *(network plot example for second-order loop)*, the quality of evidence for the indirect comparison between A vs. B was derived from the lowest quality of evidence among the 3 direct comparisons within the 2nd order loops including A vs. C (moderate), C vs. D (moderate) and D vs. B (very low). So the final quality of evidence for the indirect comparison of A vs B was adjudged to be very low. In addition, the final indirect confidence rating was rated down by one level, if there was a strong suspicion that the transitivity assumption was violated for this loop (11) Transitivity is the assumption that an indirect comparison is a valid method to compare two treatments, because the studies are sufficiently similar in important clinical and methodological characteristics, or in other words, that they are similar in their distributions of effect modifiers (12, 13).

The overall confidence in the NMA estimates for any paired comparison was rated using the higher of the confidence rating amongst the contributing direct and indirect comparisons. For example, if a NMA estimate was obtained from combining direct evidence of A vs. B that was rated as moderate, and indirect evidence of A vs. B that was rated as Low, the final A vs B NMA estimate would be rated as moderate.

Additionally, this confidence in the NMA estimate was rated down if it was found that the direct and indirect estimates had incoherence (also called inconsistency), which was defined as the differences between direct and indirect estimates of effect (10). Inconsistency was quantitatively computed using the **node-splitting model**. In a node-splitting analysis a treatment comparison is split into a parameter for direct evidence and a parameter for indirect evidence in order to assess whether there is significant disagreement between the two parameters (14). In this NMA, a node-splitting analysis was performed separately for each of the comparisons in the treatment network on which both direct and indirect evidence were available, to assess evidence consistency. A p value less than 0.05 indicated significant inconsistency between the direct and indirect comparisons. This was computed using the GeMTC GUI 0.14.3 package (15).

eFigure 4. Network meta-analysis forest plots for outcome: *PDA closure*



eFigure 4: Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for PDA closure computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

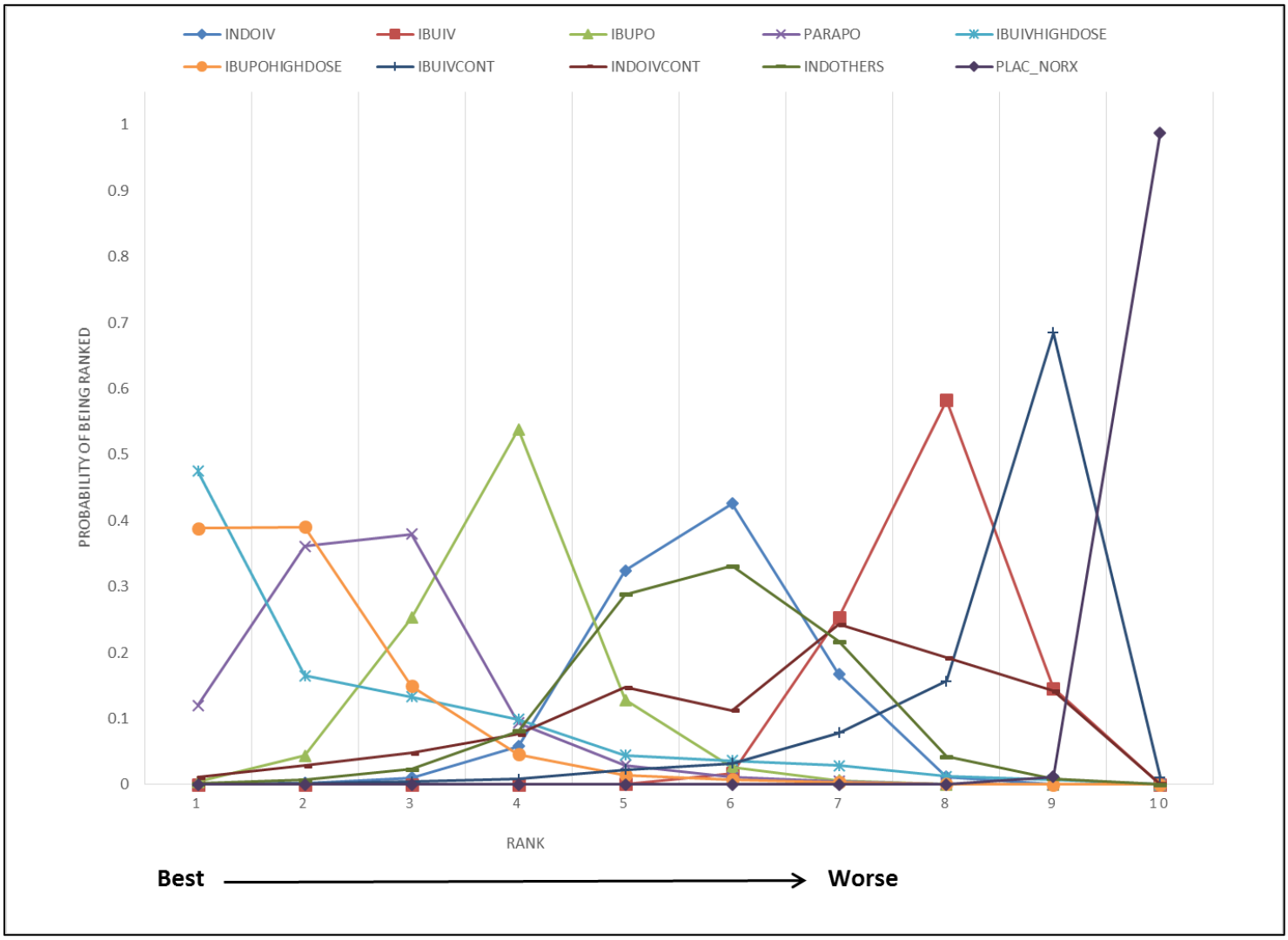
eTable 5. GRADE assessment of the Quality of Evidence (QoE) for the network for PDA closure

eTable 5.			*GRADE assessment of the Quality of Evidence (QoE) for the network for PDA closure*								
Treatment Comparison	No. of direct comparisons	Events in intervention group (n/N)	Events in comparison group (n/N)	Direct OR (95% CrI)	QoE (GRADE) based on direct comparisons	QoE (GRADE) based on indirect comparisons	Network OR (95% CrI)	Inconsistency assessment (based on node splitting p value)	Changes in GRADE assessment based on precision & effect size	Network QoE	Network absolute risk difference per 1000 infants (95% CrI)
versus INDOIV			(INDOIV)								ACR INDO IV 849/1125 (75.5%)
IBUIV	12	327/447	329/436	0.86(0.59-1.24)	MODERATE	MODERATE	0.65(0.48-0.89)	<0.01	Rated down (network inconsistency)	LOW	88 fewer (from 22 fewer to 158 fewer)
IBUPO	4	38/52	41/51	0.63(0.22-1.74)	LOW	MODERATE	1.45(0.94-2.24)	0.14	None	MODERATE	62 more (from 12 fewer to 119 more)
PARAPO	1	35/36	35/37	2.42(0.17-83.51)	MODERATE	LOW	1.92(1.00-3.68)	0.06	None	MODERATE	101 more (from 0 fewer to 164 more)
IBUIVHIGHDOSE	———	———	———	———	———	MODERATE	2.41(0.68-9.86)	———	Rated down (imprecision)	LOW	126 more (from 78 fewer to 213 more)
IBUPOHIGHDOSE	———	———	———	———	———	LOW	2.35(1.08-5.31)	———	None	LOW	124 more (from 14 more to 188 more)
IBUIVCONT	———	———	———	———	———	LOW	0.47(0.18-1.19)	———	None	LOW	164 fewer (from 31 more to 398 fewer)
INDOIVCONT	2	18/27	19/23	0.39(0.09-1.74)	LOW	LOW	0.83(0.32-2.11)	0.3	None	LOW	36 fewer (from 112 more to 259 fewer)
INDOTHERS	10	270/403	285/399	0.81(0.43-1.51)	LOW	MODERATE	0.99(0.66-1.57)	0.14	None	MODERATE	2 fewer (from 74 more to 85 fewer)
PLAC_NORX	4	112/316	140/179	0.14(0.07-0.23)	MODERATE	MODERATE	0.15(0.10-0.22)	0.94	Rated up (high precision)	HIGH	439 fewer (from 351 fewer to 519 fewer)
versus IBUIV			(IBUIV)								ACR IBUIV 542/786 (68.9%)
IBUPO	4	133/156	95/148	3.25(1.77-6.26)	HIGH	LOW	2.22(1.44-3.40)	0.11	None	HIGH	142 more (from 72 more to 194 more)
PARAPO	———	———	———	———	———	MODERATE	2.93(1.53-5.62)	———	None	MODERATE	177 more (from 83 more to 236 more)
IBUIVHIGHDOSE	1	30/35	22/35	3.82(1.07-14.71)	MODERATE	NOT ESTIMABLE	3.68(1.09-14.59)	NA	None	MODERATE	201 more (from 18 more to 281 more)
IBUPOHIGHDOSE	———	———	———	———	———	MODERATE	3.59(1.64-8.17)	———	Rated up (large effect)	HIGH	199 more (from 95 more to 258 more)
IBUIVCONT	1	27/55	32/56	0.72(0.29-1.79)	LOW	NOT ESTIMABLE	0.72(0.29-1.73)	NA	None	LOW	74 fewer (from 104 more to 298 fewer)
INDOIVCONT	1	23/31	19/32	2.02(0.61-7.00)	LOW	LOW	1.27(0.50-3.19)	0.3	None	LOW	49 more (from 163 fewer to 187 more)
INDOTHERS	———	———	———	———	———	LOW	1.51(0.95-2.56)	———	None	LOW	81 more (from 11 fewer to 161 more)
PLAC_NORX	1	32/68	47/68	0.39(0.16-0.93)	MODERATE	MODERATE	0.22(0.14-0.34)	0.16	None	MODERATE	361 fewer (from 259 fewer to 452 fewer)
versus IBUPO			(IBUPO)								ACR IBUPO 486/650 (74.8%)
PARAPO	3	105/164	102/163	1.03(0.58-1.77)	MODERATE	MODERATE	1.33(0.81-2.17)	0.02	Rated down (network inconsistency)	LOW	50 more (from 42 fewer to 118 more)
IBUIVHIGHDOSE	———	———	———	———	———	MODERATE	1.66(0.45-7.07)	———	None	MODERATE	83 more (from 176 fewer to 207 more)
IBUPOHIGHDOSE	2	45/60	31/60	3.02(1.23-7.77)	MODERATE	MODERATE	1.63(0.84-3.24)	0.16	None	MODERATE	81 more (from 34 fewer to 158 more)
IBUIVCONT	———	———	———	———	———	LOW	0.32(0.12-0.86)	———	None	LOW	261 fewer (from 29 fewer to 485 fewer)
INDOIVCONT	———	———	———	———	———	LOW	0.58(0.21-1.56)	———	None	LOW	116 fewer (from 74 more to 364 fewer)
INDOTHERS	4	53/74	65/88	0.75(0.32-1.69)	LOW	VERY LOW	0.69(0.42-1.15)	0.99	None	LOW	76 fewer (from 25 more to 193 fewer)
PLAC_NORX	4	70/133	117/131	0.11(0.05-0.22)	VERY LOW	LOW	0.10(0.06-0.16)	0.54	Rated up (high precision)	MODERATE	519 fewer (from 426 fewer to 597 fewer)

eTable 5.					*GRADE assessment of the Quality of Evidence (QoE) for the network for PDA closure*						
Treatment Comparison	No. of direct comparisons	Events in intervention group (n/N)	Events in comparison group (n/N)	Direct OR (95% CrI)	QoE (GRADE) based on direct comparisons	QoE (GRADE) based on indirect comparisons	Network OR (95% CrI)	Inconsistency assessment (based on node splitting p value)	Changes in GRADE assessment based on precision & effect size	Network QoE	Network absolute risk difference per 1000 infants (95% CrI)
											(Continued…)
versus PARAPO			(PARAPO)								ACR PARAPO 195/267 (73%)
IBUIVHIGHDOSE	———	———	———	———	———	MODERATE	1.25(0.31-5.77)	———	None	MODERATE	42 more (from 210 more to 274 fewer)
IBUPOHIGHDOSE	1	45/62	55/67	0.57(0.21-1.55)	MODERATE	MODERATE	1.23(0.62-2.48)	0.88	None	MODERATE	39 more (from 104 fewer to 140 more)
IBUIVCONT	———	———	———	———	———	LOW	0.24(0.08-0.74)	———	None	LOW	336 fewer (from 63 fewer to 552 fewer)
INDOIVCONT	———	———	———	———	———	LOW	0.43(0.14-1.32)	———	None	LOW	192 fewer (from 51 more to 455 fewer)
INDOTHERS	———	———	———	———	———	LOW	0.52(0.26-1.05)	———	None	LOW	146 fewer (from 10 more to 317 fewer)
PLAC_NORX	———	———	———	———	———	MODERATE	0.08(0.04-0.15)	———	Rated up (high precision; large effect)	HIGH	552 fewer (441 fewer to 633 fewer)
versus IBUIVHIGHDOSE			(IBUIVHIGHDOSE)								ACR IBUIVHIGHDOSE 30/35 (85.7%)
IBUPOHIGHDOSE	———	———	———	———	———	MODERATE	0.98(0.20-4.24)	———	None	MODERATE	2 fewer (from 105 more to 312 fewer)
IBUIVCONT	———	———	———	———	———	LOW	0.19(0.04-0.89)	———	None	LOW	324 fewer (from 15 fewer to 664 fewer)
INDOIVCONT	———	———	———	———	———	LOW	0.34(0.06-1.60)	———	Rated down (imprecision)	VERY LOW	186 fewer (from 49 more to 592 fewer)
INDOTHERS	———	———	———	———	———	LOW	0.41(0.10-1.57)	———	Rated down (imprecision)	VERY LOW	146 fewer (from 47 more to 482 fewer)
PLAC_NORX	———	———	———	———	———	MODERATE	0.06(0.01-0.22)	———	Rated up (large effect)	HIGH	592 fewer (from 288 fewer to 801 fewer)
versus IBUPOHIGHDOSE			(IBUPOHIGHDOSE)								ACR IBUPOHIGHDOSE 90/122 (73.8%)
IBUIVCONT	———	———	———	———	———	LOW	0.20(0.06-0.64)	———	Rated down (imprecision)	VERY LOW	378 fewer (from 95 fewer to 593 fewer)
INDOIVCONT	———	———	———	———	———	LOW	0.35(0.10-1.17)	———	Rated down (imprecision)	VERY LOW	242 fewer (from 29 more to 518 fewer)
INDOTHERS	———	———	———	———	———	LOW	0.42(0.18-0.96)	———	None	LOW	190 fewer (from 8 fewer to 441 fewer)
PLAC_NORX	———	———	———	———	———	LOW	0.06(0.03-0.14)	———	Rated up (large effect)	MODERATE	593 fewer (from 455 fewer to 660 fewer)
versus IBUIVCONT			(IBUIVCONT)								ACR IBUIVCONT 27/55 (49.1%)
INDOIVCONT	———	———	———	———	———	LOW	1.79(0.49-6.24)	———	None	LOW	142 more (from 170 fewer to 367 more)
INDOTHERS	———	———	———	———	———	LOW	2.12(0.79-5.99)	———	None	LOW	181 more (from 59 fewer to 362 more)
PLAC_NORX	———	———	———	———	———	LOW	0.31(0.12-0.84)	———	Rated down (imprecision)	VERY LOW	261 fewer (from 43 more to 387 fewer)
versus INDOIVCONT			(INDOIVCONT)								ACR INDOIVCONT 41/58 (70.7%)
INDOTHERS	____	———	———	———	———	LOW	1.19(0.44-3.40)	———	None	LOW	35 more (from 184 more to 192 fewer)
PLAC_NORX	———	———	———	———	———	LOW	0.18(0.06-0.48)	———	Rated up (high precision)	MODERATE	404 fewer (from 170 fewer to 580 fewer)
versus INDOTHERS			(INDOTHERS)								ACR INDOTHERS 380/561 (67.7%)
PLAC_NORX	5	13/80	57/84	0.09(0.04-0.22)	HIGH	LOW	0.15(0.09-0.24)	0.07	Rated up (high precision)	HIGH	438 fewer (from 342 fewer to 518 fewer)

Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk

eFigure 5. Ranking probability (rankogram) of each treatment modality for PDA closure

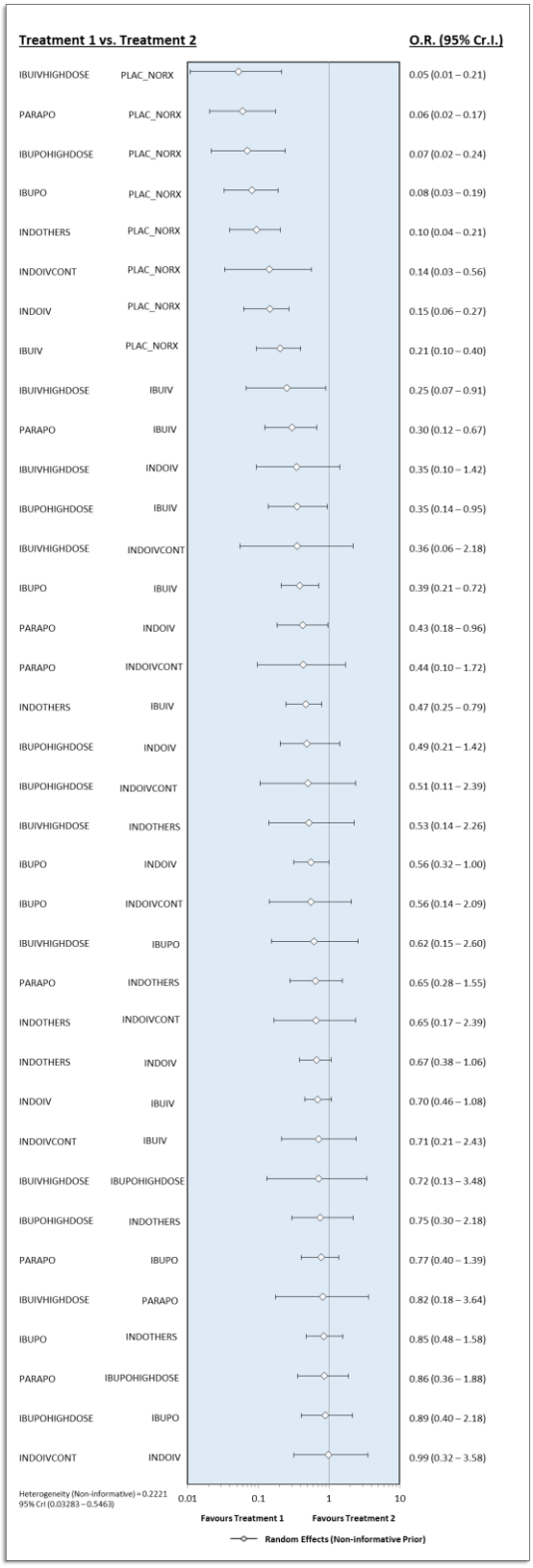


eFigure 5. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 10th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.

eTable 6. Ranking statistics for each treatment modality for outcome *PDA closure*

PDA closure		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95% Credible Intervals)**
INDOIV	0.48 (0.10)	6 (4-7)
IBUIV	0.24 (0.07)	8 (7-9)
IBUPO	0.68 (0.10)	4 (2-6)
PARAPO	0.82 (0.12)	3 (1-5)
IBUIVHIGHDOSE	0.84 (0.20)	2 (1-7)
IBUPOHIGHDOSE	0.89 (0.12)	2 (1-5)
IBUIVCONT	0.17 (0.13)	9 (5-9)
INDOIVCONT	0.40 (0.21)	7 (2-9)
INDOTHERS	0.47 (0.13)	6 (3-8)
PLAC_NORX	0.001 (0.012)	10 (10-10)

eFigure 6. Network meta-analysis forest plots for outcome: N*eed for repeat pharmacotherapy*



eFigure 6. Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for need for repeat treatment computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

eTable 7. GRADE assessment of the Quality of Evidence (QoE) for the network for need for repeat pharmacotherapy

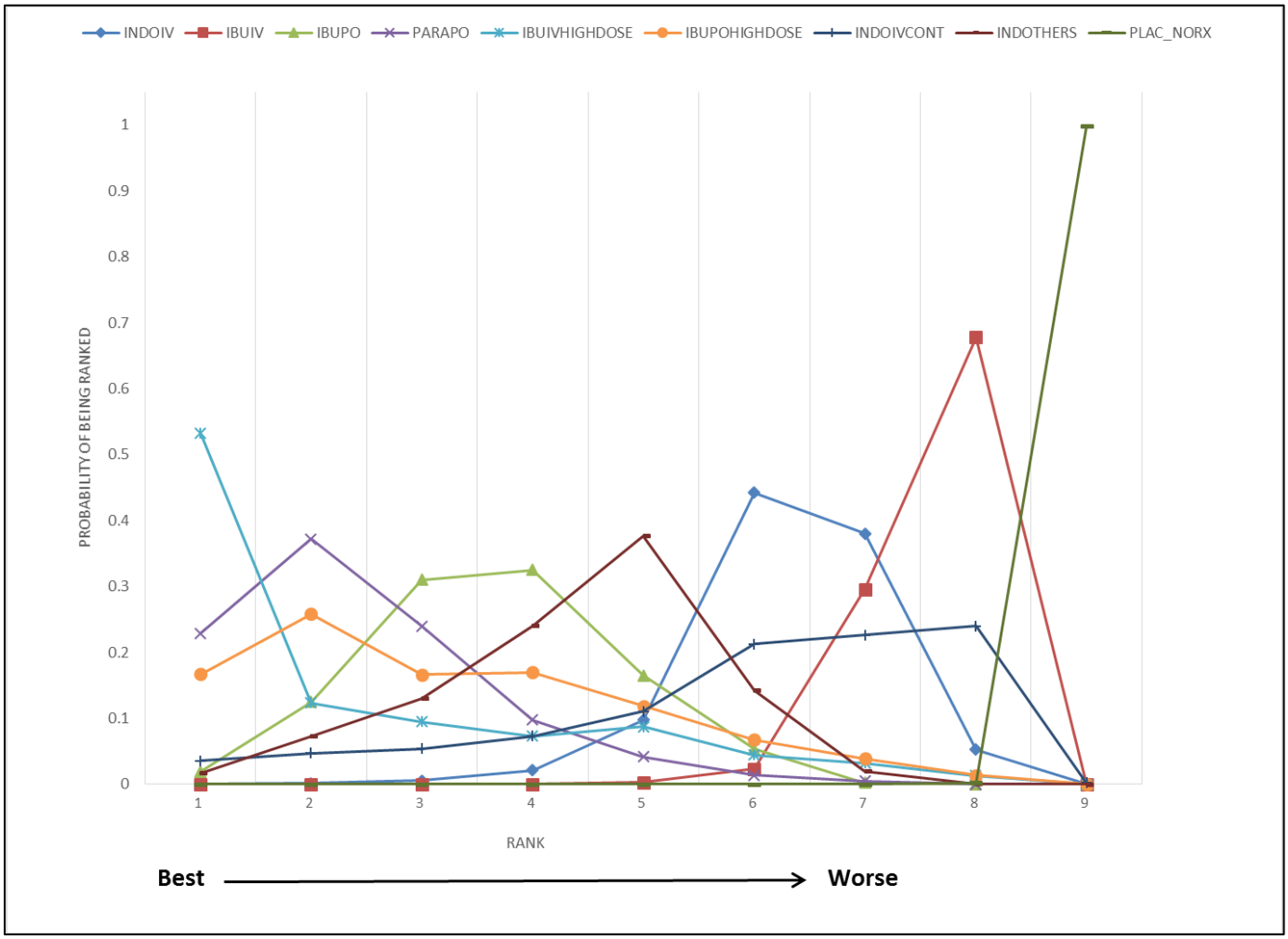
eTable 7. GRADE assessment of the Quality of Evidence (QoE) for the network for need for repeat pharmacotherapy											
Treatment Comparison	No. of direct comparisons	Events in intervention group (n/N)	Events in comparison group (n/N)	Direct OR (95% CrI)	QoE (GRADE) based on direct comparisons	QoE (GRADE) based on indirect comparisons	Network OR (95% CrI)	Inconsistency assessment (based on node splitting p value)	Changes in GRADE assessment based on precision & effect size	Network QoE	Network absolute risk difference per 1000 infants (95% CrI)
versus INDOIV			(INDOIV)								ACR INDOIV 108/601 (18%)
IBUIV	7	63/237	50/281	1.36(0.80-2.15)	MODERATE	MODERATE	1.43(0.92-2.18)	0.09	None	MODERATE	59 more (from 12 fewer to 144 more)
IBUPO	3	7/43	7/42	0.96(0.34-3.65)	LOW	MODERATE	0.56(0.32-1.00)	0.18	None	MODERATE	70 fewer (from 0 fewer to 114 fewer)
PARAPO	———			———	———	LOW	0.43(0.18-0.96)	———	None	LOW	94 fewer (from 6 fewer to 142 fewer)
IBUIVHIGHDOSE	———			———	———	MODERATE	0.35(0.10-1.42)	———	None	MODERATE	108 fewer (from 58 more to 158 fewer)
IBUPOHIGHDOSE	———			———	———	LOW	0.49(0.21-1.42)	———	None	LOW	83 fewer (from 58 more to 136 fewer)
INDOIVCONT	———			———	———	LOW	0.99(0.32-3.58)	———	None	LOW	1 fewer (from 114 fewer to 260 more)
INDOTHERS	5	30/235	42/235	0.64(0.33-1.20)	LOW	MODERATE	0.67(0.38-1.06)	———	None	MODERATE	52 fewer (from 9 more to 103 fewer)
PLAC_NORX	3	30/44	9/43	10.02(3.73-38.24)	MODERATE	MODERATE	6.87(3.66-16.03)	0.88	Rated up (large effect)	HIGH	421 more (from 265 more to 599 more)
versus IBUIV			(IBUIV)								ACR IBUIV 138/534 (25.8%)
IBUPO	3	18/124	41/116	0.34(0.16-0.61)	HIGH	LOW	0.39(0.21-0.72)	0.03	Rated down (network inconsistency)	MODERATE	139 fewer (from 58 fewer to 190 fewer)
PARAPO	———			———	———	MODERATE	0.30(0.12-0.67)	———	None	MODERATE	164 fewer (from 69 fewer to 218 fewer)
IBUIVHIGHDOSE	1	5/35	13/35	0.24(0.07-0.78)	MODERATE	NOT ESTIMABLE	0.25(0.07-0.91)	NA	None	MODERATE	178 fewer (from 18 fewer to 235 fewer)
IBUPOHIGHDOSE	———			———	———	MODERATE	0.35(0.14-0.95)	———	None	MODERATE	150 fewer (from 10 fewer to 212 fewer)
INDOIVCONT	1	9/31	12/32	0.74(0.21-2.05)	LOW	NOT ESTIMABLE	0.71(0.21-2.43)	NA	None	LOW	60 fewer (from 190 fewer to 200 more)
INDOTHERS	———			———	———	LOW	0.47(0.25-0.79)	———	None	LOW	118 fewer (from 43 fewer to 178 fewer)
PLAC_NORX	1	24/51	9/54	5.06(1.58-14.27)	MODERATE	MODERATE	4.86(2.50-10.52)	0.26	Rated up (large effect)	HIGH	370 more (from 207 more to 527 more)
versus IBUPO			(IBUPO)								ACR IBUPO 104/395 (26.3%)
PARAPO	2	31/120	34/120	0.92(0.47-1.76)	MODERATE	MODERATE	0.77(0.40-1.39)	0.99	None	MODERATE	47 fewer (from 69 more to 138 fewer)
IBUIVHIGHDOSE	———			———	———	MODERATE	0.62(0.15-2.60)	———	None	MODERATE	82 fewer (from 212 fewer to 218 more)
IBUPOHIGHDOSE	1	6/30	10/30	0.47(0.16-1.93)	MODERATE	MODERATE	0.89(0.40-2.18)	0.38	None	MODERATE	22 fewer (from 138 fewer to 175 more)
INDOIVCONT	———			———	———	LOW	1.79(0.48-7.00)	———	None	LOW	127 more (from 117 fewer to 451 more)
INDOTHERS	3	26/64	35/78	0.91(0.45-2.54)	LOW	VERY LOW	1.18(0.63-2.08)	0.89	None	LOW	33 more (from 80 fewer to 163 more)
PLAC_NORX	———			———	———	LOW	12.24(5.25-30.54)	———	Rated up (large effect)	MODERATE	551 more (from 389 more to 653 more)
versus PARAPO			(PARAPO)								ACR PARAPO 43/187 (23%)
IBUIVHIGHDOSE	———			———	———	MODERATE	0.82(0.18-3.64)	———	None	MODERATE	33 fewer (from 179 fewer to 291 more)
IBUPOHIGHDOSE	1	17/62	12/67	1.95(0.69-4.69)	MODERATE	MODERATE	1.16(0.53-2.76)	0.62	None	MODERATE	27 more (from 93 fewer to 222 more)
INDOIVCONT	———			———	———	LOW	2.30(0.58-10.14)	———	Rated down (imprecision)	VERY LOW	177 more (from 82 fewer to 522 more)
INDOTHERS	———			———	———	LOW	1.53(0.64-3.55)	———	None	LOW	84 more (from 69 fewer to 285 more)
PLAC_NORX	———			———	———	MODERATE	16.58(5.72-48.36)	———	Rated up (large effect)	HIGH	602 more (from 401 more to 705 more)
versus IBUIVHIGHDOSE			(IBUIVHIGHDOSE)								ACR IBUIVHIGHDOSE 5/35 (14.3%)
IBUPOHIGHDOSE	———			———	———	MODERATE	1.39(0.29-7.61)	———	None	MODERATE	45 more (from 97 fewer to 416 more)
INDOIVCONT	———			———	———	LOW	2.80(0.46-18.15)	———	Rated down (imprecision)	VERY LOW	175 more (from 72 fewer to 609 more)
INDOTHERS	———			———	———	LOW	1.90(0.44-7.08)	———	None	LOW	98 more (from 75 fewer to 398 more)
PLAC_NORX	———			———	———	MODERATE	18.97(4.69-92.05)	———	Rated up (large effect)	HIGH	617 more (from 296 more to 796 more)
versus IBUPOHIGHDOSE			(IBUPOHIGHDOSE)								ACR IBUPOHIGHDOSE 23/92 (25%)
INDOIVCONT	———			———	———	LOW	1.98(0.42-9.38)	———	None	LOW	148 more (from 127 fewer to 508 more)
INDOTHERS	———			———	———	LOW	1.33(0.46-3.34)	———	None	LOW	57 more (from 117 fewer to 277 more)
PLAC_NORX	———			———	———	LOW	14.17(4.16-46.11)	———	Rated up (large effect)	MODERATE	575 more (from 331 more to 689 more)

eTable 7. GRADE assessment of the Quality of Evidence (QoE) for the network for need for repeat pharmacotherapy

Treatment Comparison	No. of direct comparisons	Events in intervention group (n/N)	Events in comparison group (n/N)	Direct OR (95% CrI)	QoE (GRADE) based on direct comparisons	QoE (GRADE) based on indirect comparisons	Network OR (95% CrI)	Inconsistency assessment (based on node splitting p value)	Changes in GRADE assessment based on precision & effect size	Network QoE	Network absolute risk difference per 1000 infants (95% CrI)
(Continued…)											
versus INDOIVCONT			(INDOIVCONT)								ACR INDOIVCONT 9/31 (29%)
INDOTHERS	———			———	———	LOW	0.65(0.17-2.39)	———	None	LOW	80 fewer (from 204 more to 225 fewer)
PLAC_NORX	———			———	———	LOW	6.98(1.77-29.85)	———	Rated up (large effect)	MODERATE	450 more (from 130 more to 634 more)
versus INDOTHERS			(INDOTHERS)								ACR INDOTHERS 62/326 (19%)
PLAC_NORX	2	15/26	6/27	4.92(1.68-21.35)	HIGH	LOW	10.52(4.86-25.32)	0.1	None	HIGH	522 more (from 343 more to 666 more)

Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk

eFigure 7. Ranking probability (rankogram) of each treatment modality for need for repeat pharmacotherapy

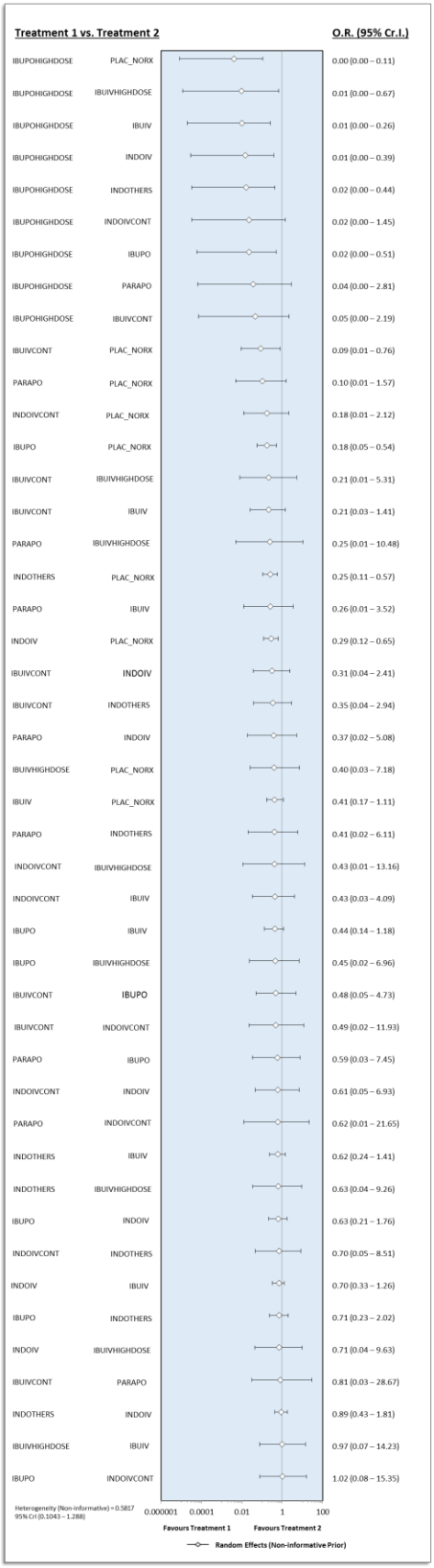


eFigure 7. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 9th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.

eTable 8. Ranking statistics for each treatment modality for outcome need for repeat pharmacotherapy

Need for repeat pharmacotherapy		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95% Credible Intervals)**
INDOIV	0.33 (0.11)	6 (4-8)
IBUIV	0.17 (0.07)	8 (6-8)
IBUPO	0.67 (0.14)	4 (2-6)
PARAPO	0.82 (0.15)	2 (1-5)
IBUIVHIGHDOSE	0.83 (0.24)	1 (1-7)
IBUPOHIGHDOSE	0.72 (0.22)	3 (1-7)
INDOIVCONT	0.38 (0.24)	6 (1-8)
INDOTHERS	0.58 (0.16)	5 (2-6)
PLAC_NORX	0.0003 (0.0056)	9 (9-9)

eFigure 8. Network meta-analysis forest plots for outcome: N*eed for surgical PDA ligation*



eFigure 8: Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for need for surgical PDA ligation computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

eTable 9. GRADE assessment of the Quality of Evidence (QoE) for the network for need for surgical PDA ligation

eTable 9. **GRADE assessment of the Quality of Evidence (QoE) for the network for need for surgical PDA ligation**											
Treatment Comparison	No. of direct comparisons	Events in the intervention group (n/N)	Events in the comparison group (n/N)	Direct OR (95% CrI)	QoE (GRADE) based on direct comparisons	QeE (GRADE) based on indirect comparisons	Network OR (95% CrI)	Inconsistency assessment (based on node splitting p value)	Changes in GRADE assessment based on precision & effect size	Network QoE	Network absolute risk difference per 1000 infants (95% CrI)
versus INDOIV			(INDOIV)								ACR INDOIV 92/767 (12%)
IBUIV	8	52/376	50/365	1.15 (0.61-2.77)	MODERATE	MODERATE	1.42(0.79-3.01)	0.56	None	MODERATE	42 more (from 23 fewer to 171 more)
IBUPO	1	1/16	2/18	0.47 (0.01-8.65)	LOW	MODERATE	0.62(0.20-1.76)	0.43	None	MODERATE	42 fewer (from 74 more to 93 fewer)
PARAPO	1	0/36	0/37	0.93 (0.00-541)	MODERATE	LOW	0.37(0.01-5.08)	0.72	Rated down (imprecision)	LOW	72 fewer (from 119 fewer to 289 more)
IBUIVHIGHDOSE	———			———	———	MODERATE	1.40(0.10-22.8)	———	Rated down (imprecision)	LOW	40 more (from 107 fewer to 637 more)
IBUPOHIGHDOSE	———			———	———	LOW	0.014(0.00-0.38)	———	None	LOW	118 fewer (up to 71 fewer)*
IBUIVCONT	———			———	———	LOW	0.30(0.03-2.41)	———	None	LOW	81 fewer (from 115 fewer to 127 more)
INDOIVCONT	———			———	LOW	LOW	0.61(0.04-6.92)	———	None	LOW	43 fewer (from 115 fewer to 365 more)
INDOTHERS	5	42/237	37/232	1.14 (0.47-2.73)	LOW	MODERATE	0.88(0.43-1.81)	0.56	None	MODERATE	13 fewer (from 65 fewer to 78 more)
PLAC_NORX	5	10/119	3/115	4.10 (0.83-23.68)	MODERATE	MODERATE	3.49(1.53-8.34)	0.17	None	MODERATE	202 more (from 53 more to 412 more)
versus IBUIV			(IBUIV)								ACR IBUIV 86/715 (12%)
IBUPO	4	3/156	9/148	0.26 (0.04-1.25)	HIGH	LOW	0.44(0.13-1.17)	0.73	None	HIGH	64 fewer (from 18 more to 103 fewer)
PARAPO	———			———	———	MODERATE	0.25(0.01-3.51)	———	Rated down (imprecision)	LOW	87 fewer (from 119 fewer to 204 more)
IBUIVHIGHDOSE	1	2/35	2/35	0.98 (0.06-14.73)	MODERATE	NOT ESTIMABLE	0.97(0.07-14.2)	NA	Rated down (imprecision)	LOW	3 fewer (from 111 fewer to 540 more)
IBUPOHIGHDOSE	———			———	———	MODERATE	0.01(0.00-0.26)	———	None	MODERATE	119 fewer (up to 86 fewer)*
IBUIVCONT	1	3/55	11/56	0.21 (0.03-1.42)	LOW	NOT ESTIMABLE	0.21(0.02-1.41)	NA	Rated down (imprecision)	VERY LOW	92 fewer (from 41 more to 118 fewer)
INDOIVCONT	1	2/31	4/32	0.43 (0.03-4.33)	LOW	NOT ESTIMABLE	0.42(0.03-4.09)	NA	Rated down (imprecision)	VERY LOW	66 fewer (from 116 fewer to 238 more)
INDOTHERS	———			———	———	LOW	0.62(0.23-1.41)	———	None	LOW	42 fewer (from 41 more to 90 fewer)
PLAC_NORX	1	9/68	8/68	1.10 (0.19-6.78)	MODERATE	MODERATE	2.44(0.9-6.0)	0.7	None	MODERATE	130 more (from 11 fewer to 330 more)
versus IBUPO			(IBUPO)								ACR IBUPO 26/354 (7.3%)
PARAPO	1	1/40	2/40	0.39 (0.00-7.69)	MODERATE	LOW	0.59(0.03-7.45)	0.78	Rated down (imprecision)	LOW	29 fewer (from 71 fewer to 298 more)
IBUIVHIGHDOSE	———			———	———	MODERATE	2.22(0.14-42.88)	———	None	MODERATE	76 more (from 62 fewer to 699 more)
IBUPOHIGHDOSE	1	0/30	7/30	0.02 (0.00 - 0.47)	MODERATE	NOT ESTIMABLE	0.02(0.00-0.50)	NA	None	MODERATE	72 fewer (up to 35 fewer)*
IBUIVCONT	———			———	———	LOW	0.48(0.05-4.72)	———	Rated down (imprecision)	VERY LOW	37 fewer (from 69 fewer to 199 more)
INDOIVCONT	———			———	———	LOW	0.97(0.06-12.96)	———	Rated down (imprecision)	VERY LOW	2 fewer (from 69 fewer to 433 more)
INDOTHERS	1	7/35	12/48	0.73 (0.12-4.42)	LOW	VERY LOW	1.40(0.49-4.31)	0.11	None	LOW	26 more (from 36 fewer to 181 more)
PLAC_NORX	2	8/64	1/64	11.52 (1.05-307)	VERY LOW	LOW	5.54(1.86-18.2)	0.99	Rated down (imprecision)	VERY LOW	232 more (from 55 more to 517 more)
versus PARAPO			(PARAPO)								ACR PARAPO 1/76 (1.3%)
IBUIVHIGHDOSE	———			———	———	MODERATE	3.96(0.09-199.3)	———	Rated down (imprecision)	LOW	37 more (from 12 fewer to 713 more)
IBUPOHIGHDOSE	———			———	———	LOW	0.03(0.00-2.80)	———	Rated down (imprecision)	VERY LOW	13 fewer (from – to 23 more)*
IBUIVCONT	———			———	———	LOW	0.81(0.03-28.6)	———	Rated down (imprecision)	VERY LOW	2 fewer (from 13 fewer to 263 more)
INDOIVCONT	———			———	———	LOW	1.61(0.04-77.34)	———	Rated down (imprecision)	VERY LOW	8 more (from 13 fewer to 495 more)
INDOTHERS	———			———	———	LOW	2.41(0.16-48.33)	———	Rated down (imprecision)	VERY LOW	18 more (from 11 fewer to 379 more)
PLAC_NORX	———			———	———	MODERATE	9.54(0.63-197.9)	———	Rated down (imprecision)	LOW	100 more (from 5 fewer to 712 more)

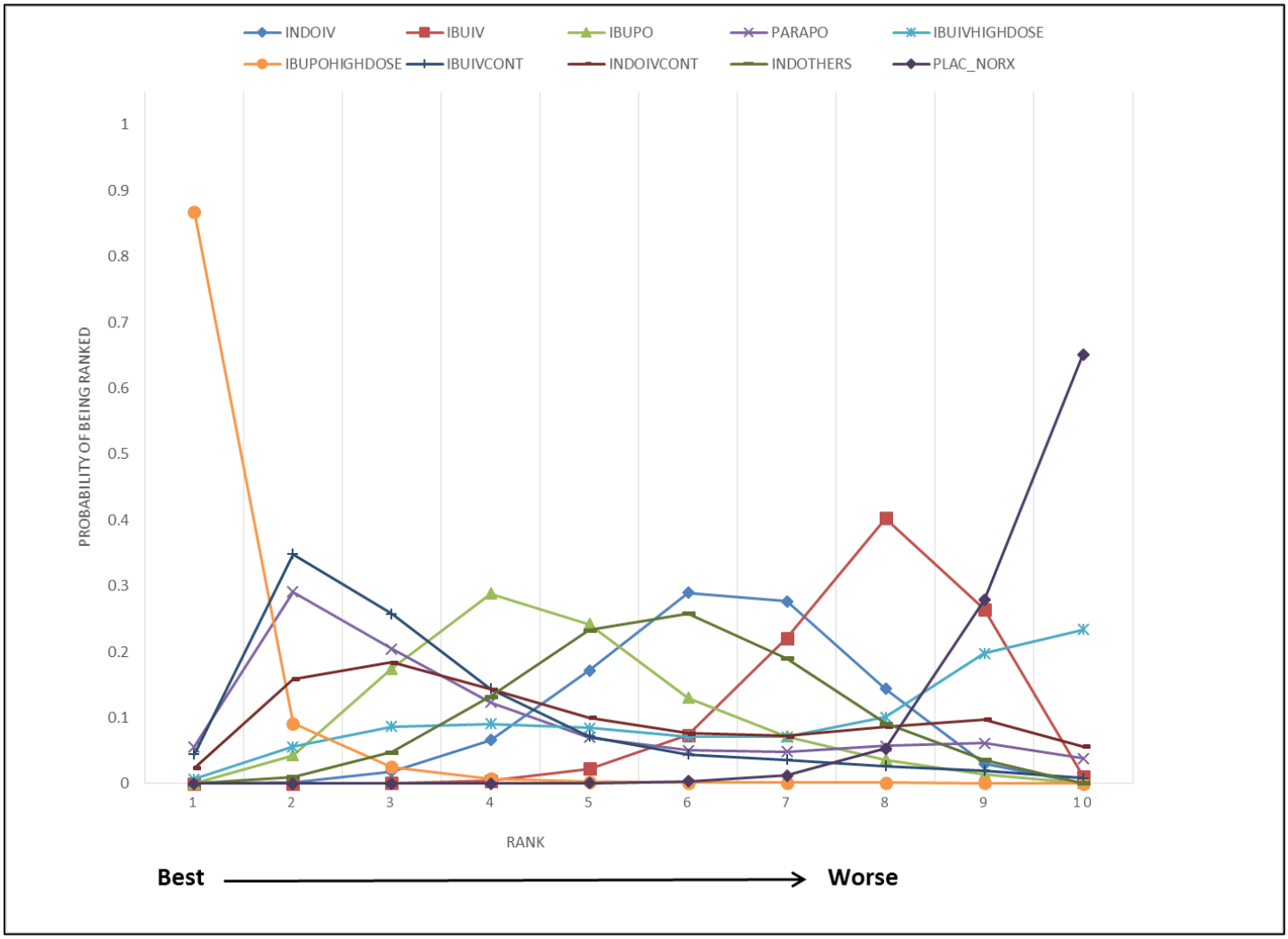
eTable 9. **GRADE assessment of the Quality of Evidence (QoE) for the network for need for surgical PDA ligation**											
Treatment Comparison	No. of direct comparisons	Events in the intervention group (n/N)	Events in the comparison group (n/N)	Direct OR (95% CrI)	QoE (GRADE) based on direct comparisons	QeE (GRADE) based on indirect comparisons	Network OR (95% CrI)	Inconsistency assessment (based on node splitting p value)	Changes in GRADE assessment based on precision & effect size	Network QoE	Network absolute risk difference per 1000 infants (95% CrI)
											(…..Continued)
versus IBUIVHIGHDOSE			(IBUIVHIGHDOSE)								ACR IBUIVHIGHDOSE 2/35 (5.7%)
IBUPOHIGHDOSE	———			———	———	MODERATE	0.01(0.00-0.67)	———	None	MODERATE	57 fewer (up to 18 fewer)*
IBUIVCONT	———			———	———	LOW	0.20(0.00-5.3)	———	Rated down (imprecision)	VERY LOW	45 fewer (from – to 186 more)*
INDOIVCONT	———			———	———	LOW	0.421(0.01-13.16)	———	Rated down (imprecision)	VERY LOW	32 fewer (from 57 fewer to 387 more)
INDOTHERS	———			———	———	LOW	0.62(0.03-9.25)	———	Rated down (imprecision)	VERY LOW	21 fewer (from 55 fewer to 302 more)
PLAC_NORX	———			———	———	MODERATE	2.49(0.13-37.36)	———	Rated down (imprecision)	LOW	74 more (from 49 fewer to 637 more)
versus IBUPOHIGHDOSE			(IBUPOHIGHDOSE)								ACR IBUPOHIGHDOSE 0/30 (0%) **
IBUIVCONT	———			———	———	LOW	21.75(0.456-14340)	———	Rated down (imprecision)	VERY LOW	253 more (from 9 fewer to 979 more)
INDOIVCONT	———			———	———	LOW	44.04(0.68-30690)	———	Rated down (imprecision)	VERY LOW	411 more (from 5 fewer to 981 more)
INDOTHERS	———			———	———	LOW	61.43(2.27-30340)	———	Rated up (large effect)	MODERATE	493 more (from 20 more to 981 more)
PLAC_NORX	———			———	———	LOW	242.4(9.11-122400)	———	Rated up (large effect)	MODERATE	788 more (from 117 more to 983 more)
versus IBUIVCONT			(IBUIVCONT)								ACR IBUIVCONT 3/55 (5.5%)
INDOIVCONT	———			———	———	LOW	2.042(0.08-43.79)	———	Rated down (imprecision)	VERY LOW	51 more (from 50 fewer to 662 more)
INDOTHERS	———			———	———	LOW	2.894(0.33-25.56)	———	Rated down (imprecision)	VERY LOW	88 more (from 36 fewer to 541 more)
PLAC_NORX	———			———	———	LOW	11.55(1.32-106.2)	———	Rated down (imprecision)	VERY LOW	354 more (from 16 more to 805 more)
versus INDOIVCONT			(INDOIVCONT)								ACR INDOIVCONT 2/31 (6.5%)
INDOTHERS	———			———	———	LOW	1.428(0.11-21.0)	———	Rated down (imprecision)	VERY LOW	25 more (from 57 fewer to 527 more)
PLAC_NORX	———			———	———	LOW	5.677(0.47-81.8)	———	Rated down (imprecision)	VERY LOW	217 more (from 33 fewer to 785 more)
versus INDOTHERS			(INDOTHERS)								ACR INDOTHERS 61/345 (17.7%)
PLAC_NORX	4	33/70	12/73	5.15 (1.64-14.61)	HIGH	LOW	3.96 (1.75-9.0)	0.14	None	VERY LOW	283 more (from 96 more to 482 more)

Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk

*The lower limit of the 95% credible interval for absolute risk difference could not be computed due to the very low (tending to zero) lower limit of the 95% credible interval for the corresponding network odds ratio

**In view of zero event rate for the particular outcome in the control group, a continuity correction of 0.5 has been applied to calculate the assumed control risk in order to compute the absolute risk difference (16).

eFigure 9. Ranking probability (rankogram) of each treatment modality for need for surgical PDA ligation

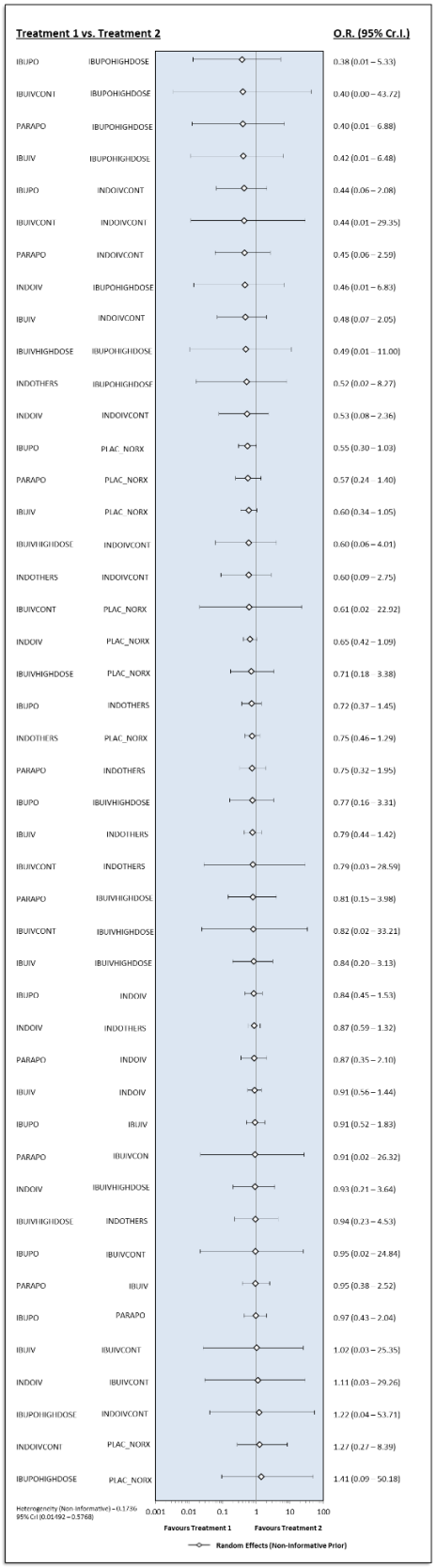


eFigure 9. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 10th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.

eTable 10. Ranking statistics for each treatment modality for need for surgical PDA ligation

Need for surgical PDA ligation		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95% Credible intervals)**
INDOIV	0.41 (0.14)	6 (4-9)
IBUIV	0.24 (0.12)	8 (5-9)
IBUPO	0.59 (0.17)	4 (2-8)
PARAPO	0.65 (0.28)	3 (1-10)
IBUIVHIGHDOSE	0.33 (0.30)	8 (2-10)
IBUPOHIGHDOSE	0.98 (0.08)	1 (1-3)
IBUIVCONT	0.73 (0.21)	3 (1-9)
INDOIVCONT	0.55 (0.29)	4 (2-10)
INDOTHERS	0.47 (0.17)	6 (3-9)
PLAC_NORX	0.05 (0.08)	10 (8-10)

eFigure 10. Network meta-anlaysis forest plots for outcome: *Neonatal Mortality*



eFigure 10. Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for neonatal mortality computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

eTable 11. GRADE assessment of the Quality of Evidence (QoE) for the network for Neonatal Mortality

eTable 11. GRADE assessment of the Quality of Evidence (QoE) for the network for Neonatal Mortality

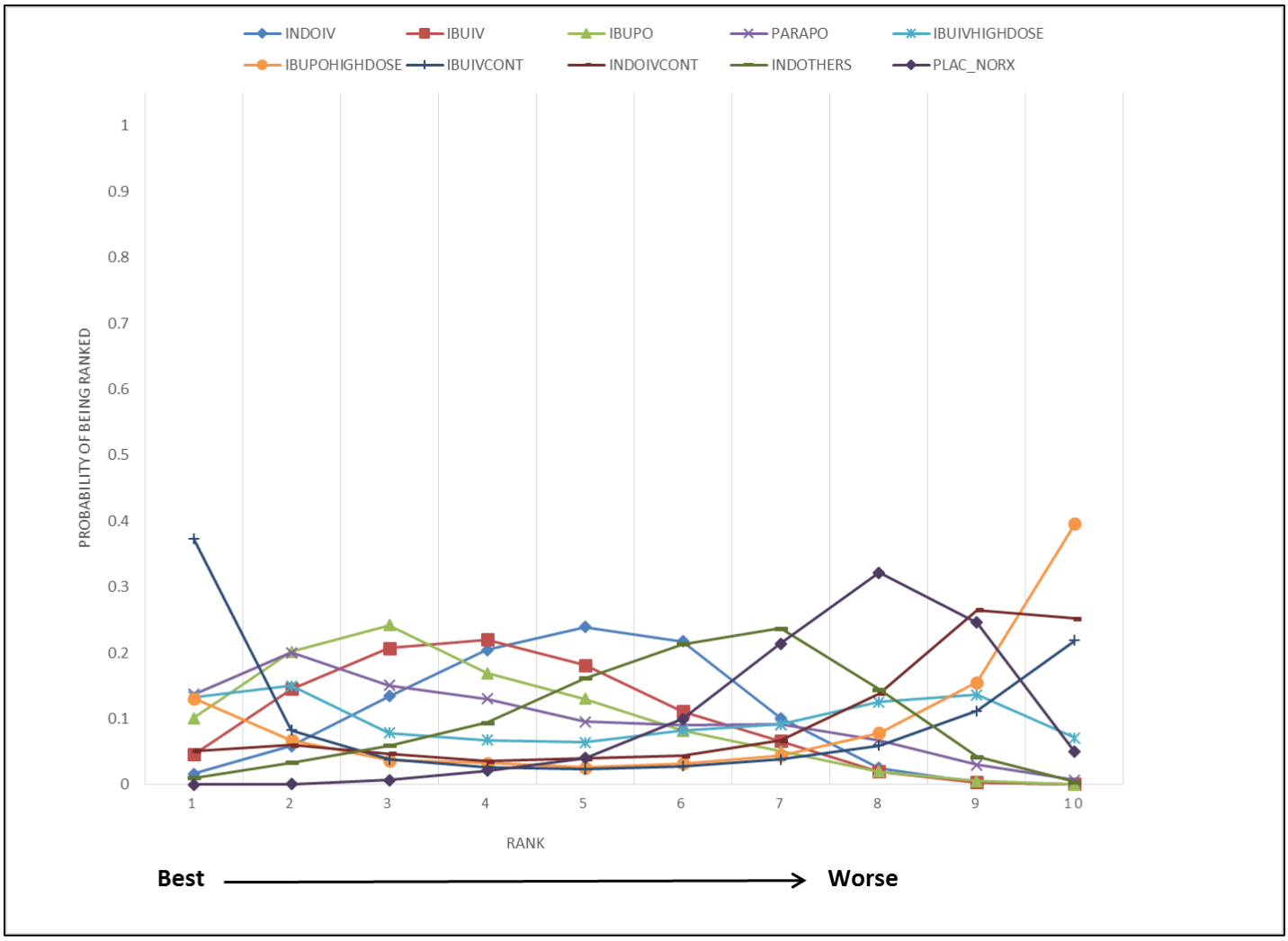
Treatment Comparison	No. of direct comparisons	Events in the intervention group (n/N)	Events in the comparison group (n/N)	Direct OR (95% CrI)	QoE (GRADE) based on direct comparisons	QoE (GRADE) based on indirect comparisons	Network OR (95% CrI)	Inconsistency assessment (based on node splitting p value)	Changes in GRADE assessment based on precision & effect size	Network QoE	Network absolute risk difference per 1000 infants (95% CrI)
versus INDOIV			(INDOIV)								ACR INDO IV 111/904 (12.3%)
IBUIV	6	29/303	29/289	0.90 (0.49-1.65)	MODERATE	MODERATE	0.91(0.56-1.44)	0.56	None	MODERATE	10 fewer (from 45 more to 50 fewer)
IBUPO	3	4/40	5/42	0.68(0.12-3.57)	LOW	MODERATE	0.84(0.45-1.53)	0.43	None	MODERATE	18 fewer (from 54 more to 64 fewer)
PARAPO	1	8/38	8/39	0.99 (0.28-3.49)	MODERATE	LOW	0.87(0.35-2.10)	0.72	None	MODERATE	14 fewer (from 76 fewer to 104 more)
IBUIVHIGHDOSE	———			———	———	MODERATE	1.07(0.27-4.81)	———	None	MODERATE	7 more (from 86 fewer to 280 more)
IBUPOHIGHDOSE	———			———	———	LOW	2.19(0.15-72.38)	———	Rated down (Imprecision)	VERY LOW	112 more (from 102 fewer to 787 more)
IBUIVCONT	———			———	———	LOW	0.90(0.03-33.65)	———	Rated down (Imprecision)	VERY LOW	11 fewer (from 119 fewer to 702 more)
INDOIVCONT	1	2/18	0/14	1.89 (0.74-8.89)	LOW	LOW	1.89(0.42-12.82)	0.66	Rated down (Imprecision)	VERY LOW	86 more (from 67 fewer to 519 more)
INDOTHERS	7	52/359	42/358	1.31(0.79-2.13)	LOW	MODERATE	1.15(0.76-1.70)	0.2	None	MODERATE	16 more (from 27 fewer to 69 more)
PLAC_NORX	7	30/169	27/162	1.11 (0.58-2.11)	MODERATE	MODERATE	1.53(0.92-2.36)	0.17	None	MODERATE	54 more (from 9 fewer to 126 more)
versus IBUIV			(IBUIV)								ACR IBUIV 60/664 (9%)
IBUPO	3	13/120	10/116	1.41 (0.51-3.99)	HIGH	LOW	0.91(0.52-1.83)	0.73	None	LOW	7 fewer (from 41 fewer to 63 more)
PARAPO	———			———	———	MODERATE	0.95(0.38-2.52)	———	None	MODERATE	4 fewer (from 54 fewer to 110 more)
IBUIVHIGHDOSE	1	6/35	5/35	1.24 (0.31-5.35)	MODERATE	NOT ESTIMABLE	1.20(0.32-5.06)	NA	None	MODERATE	16 more (from 60 fewer to 244 more)
IBUPOHIGHDOSE	———			———	———	MODERATE	2.39(0.15-88.03)	———	Rated down (Imprecision)	LOW	102 more (from 76 fewer to 807 more)
IBUIVCONT	1	1/55	1/56	0.93 (0.03-24.45)	LOW	NOT ESTIMABLE	0.98(0.04-38.00)	NA	Rated down (Imprecision)	VERY LOW	2 fewer (from 86 fewer to 700 more)
INDOIVCONT	1	4/31	3/32	1.36 (0.26-8.44)	LOW	LOW	2.09(0.49-14.65)	0.78	Rated down (Imprecision)	VERY LOW	82 more (from 44 fewer to 502 more)
INDOTHERS	———			———	———	LOW	1.27(0.70-2.25)	———	None	LOW	22 more (from 25 fewer to 92 more)
PLAC_NORX	2	16/119	12/122	1.45 (0.59-3.46)	MODERATE	MODERATE	1.67(0.95-2.92)	0.7	None	MODERATE	52 more (from 4 fewer to 134 more)
versus IBUPO			(IBUPO)								ACR IBUPO 43/484 (8.9%)
PARAPO	2	13/120	14/120	0.92 (0.36-2.49)	MODERATE	LOW	1.03(0.49-2.34)	0.78	None	LOW	2 more (from 43 fewer to 97 more)
IBUIVHIGHDOSE	———			———	———	MODERATE	1.30(0.30-6.08)	———	None	MODERATE	24 more (from 60 fewer to 283 more)
IBUPOHIGHDOSE	1	2/30	1/30	2.59 (0.25-42.94)	MODERATE	NOT ESTIMABLE	2.61(0.19-76.13)	NA	Rated down (Imprecision)	LOW	114 more (from 71 fewer to 792 more)
IBUIVCONT	———			———	———	LOW	1.05(0.04-46.64)	———	Rated down (Imprecision)	VERY LOW	4 more (from 85 fewer to 731 more)
INDOIVCONT	———			———	———	LOW	2.30(0.48-15.43)	———	Rated down (Imprecision)	VERY LOW	94 more (from 44 fewer to 512 more)
INDOTHERS	3	8/64	3/78	3.92 (1.03-17.37)	LOW	VERY LOW	1.38(0.69-2.70)	0.01	Rated down (Incoherence)	VERY LOW	30 more (from 26 fewer to 120 more)
PLAC_NORX	3	12/96	8/96	1.62 (0.60-4.68)	VERY LOW	LOW	1.81(0.97-3.31)	0.99	None	LOW	61 more (from 2 fewer to 155 more)
versus PARAPO			(PARAPO)								ACR PARAPO 21/158 (13.3%)
IBUIVHIGHDOSE	———			———	———	MODERATE	1.24(0.25-6.83)	———	None	MODERATE	27 more (from 96 fewer to 379 more)
IBUPOHIGHDOSE	———			———	———	LOW	2.47(0.15-80.63)	———	Rated down (Imprecision)	VERY LOW	142 more (from 110 fewer to 792 more)
IBUIVCONT	———			———	———	LOW	1.09(0.04-45.81)	———	Rated down (Imprecision)	VERY LOW	10 more (from 127 fewer to 742 more)
INDOIVCONT	———			———	———	LOW	2.20(0.39-16.46)	———	Rated down (Imprecision)	VERY LOW	119 more (from 77 fewer to 583 more)
INDOTHERS	———			———	———	LOW	1.33(0.51-3.09)	———	None	LOW	36 more (from 60 fewer to 189 more)
PLAC_NORX	———			———	———	MODERATE	1.74(0.72-4.16)	———	None	MODERATE	78 more (from 34 fewer to 256 more)

eTable 11. GRADE assessment of the Quality of Evidence (QoE) for the network for Neonatal Mortality

Treatment Comparison	No. of direct comparisons	Events in the intervention group (n/N)	Events in the comparison group (n/N)	Direct OR (95% CrI)	QoE (GRADE) based on direct comparisons	QoE (GRADE) based on indirect comparisons	Network OR (95% CrI)	Inconsistency assessment (based on node splitting p value)	Changes in GRADE assessment based on precision & effect size	Network QoE	Network absolute risk difference per 1000 infants (95% CrI)
(…continued)											
versus IBUIVHIGHDOSE			(IBUIVHIGHDOSE)								ACR IBUIVHIGHDOSE 6/35 (17.1%)
IBUPOHIGHDOSE	———			———	———	MODERATE	2.04(0.09-92.38)	———	Rated down (Imprecision)	LOW	125 more (from 153 fewer to 779 more)
IBUIVCONT	———			———	———	LOW	0.82(0.02-33.21)	———	Rated down (Imprecision)	VERY LOW	26 fewer (from 167 fewer to 702 more)
INDOIVCONT	———			———	———	LOW	1.67(0.25-16.18)	———	Rated down (Imprecision)	VERY LOW	85 more (from 122 fewer to 599 more)
INDOTHERS	———			———	———	LOW	1.07(0.22-4.31)	———	None	VERY LOW	10 more (from 128 fewer to 300 more)
PLAC_NORX	———			———	———	MODERATE	1.40(0.30-5.71)	———	None	MODERATE	53 more (from 113 fewer to 370 more)
versus IBUPOHIGHDOSE			(IBUPOHIGHDOSE)								ACR IBUPOHIGHDOSE 2/30 (6.7%)
IBUIVCONT	———			———	———	LOW	0.40(0.00-43.72)	———	Rated down (Imprecision)	VERY LOW	39 fewer (from – to 691 more)*
INDOIVCONT	———			———	———	LOW	0.82(0.02-24.35)	———	Rated down (Imprecision)	VERY LOW	11 fewer (from 65 fewer to 568 more)
INDOTHERS	———			———	———	LOW	0.52(0.02-8.27)	———	None	LOW	31 fewer (from 65 fewer to 305 more)
PLAC_NORX	———			———	———	LOW	0.71(0.02-10.63)	———	Rated down (Imprecision)	VERY LOW	18 fewer (from 65 fewer to 365 more)
versus IBUIVCONT			(IBUIVCONT)								ACR IBUIVCONT 1/55 (1.8%)
INDOIVCONT	———			———	———	LOW	2.26(0.03-87.92)	———	Rated down (Imprecision)	VERY LOW	22 more (from 18 fewer to 601 more)
INDOTHERS	———			———	———	LOW	1.27(0.03-36.40)	———	Rated down (Imprecision)	VERY LOW	5 more (from 18 fewer to 384 more)
PLAC_NORX	———			———	———	LOW	1.64(0.04-48.25)	———	Rated down (Imprecision)	VERY LOW	11 more (from 17 fewer to 454 more)
versus INDOIVCONT			(INDOIVCONT)								ACR INDOIVCONT 6/49 (12.2%)
INDOTHERS	———			———	———	LOW	0.60(0.09-2.75)	———	None	LOW	7 fewer (from 17 fewer to 30 more)
PLAC_NORX	———			———	———	LOW	0.78(0.12-3.71)	———	None	LOW	4 fewer (from 16 fewer to 46 more)
versus INDOTHERS			(INDOTHERS)								ACR INDOTHERS 69/496 (13.9%)
PLAC_NORX	4	21/70	9/73	3.15 (1.24-8.26)	HIGH	LOW	1.33(0.78-2.19)	0.14	None	LOW	38 more (from 27 fewer to 122 more)

Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk
*The lower limit of the 95% credible interval for absolute risk difference could not be computed due to the very low (tending to zero) lower limit of the 95% credible interval for the corresponding network odds ratio

eFigure 11. Ranking probability (rankogram) of each treatment modality for Neonatal Mortality

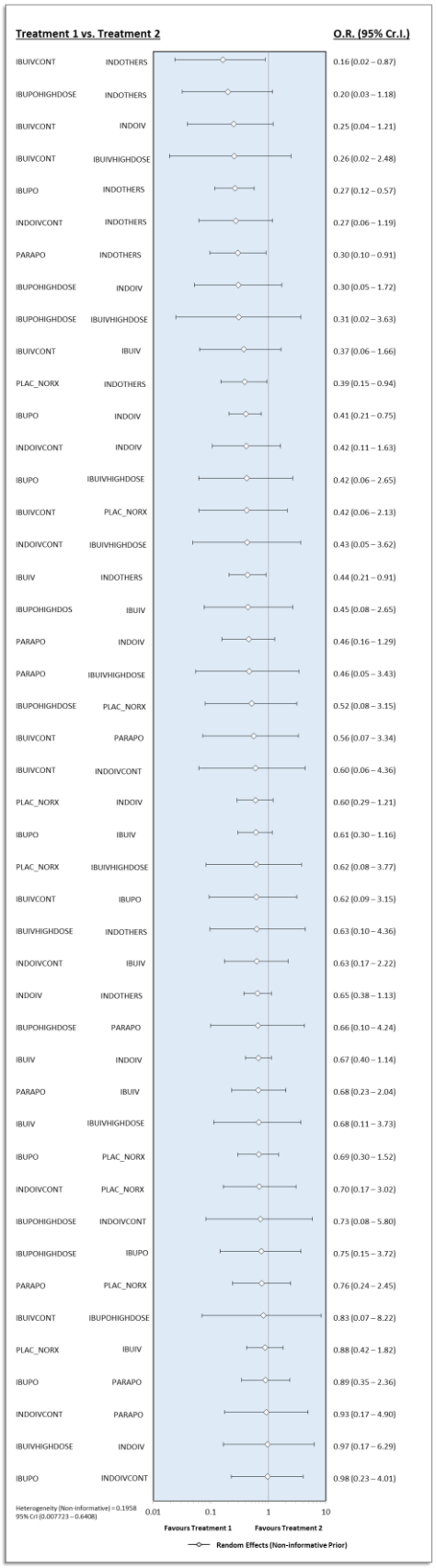


eFigure 11. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 10th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.

eTable 12. Ranking statistics for each treatment modality for Neonatal Mortality

Neonatal Mortality		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95% Credible Intervals)**
INDOIV	0.58 (0.17)	5 (2-8)
IBUIV	0.66 (0.19)	4 (1-7)
IBUPO	0.71 (0.20)	3 (1-8)
PARAPO	0.66 (0.26)	4 (1-9)
IBUIVHIGHDOSE	0.52 (0.34)	6 (1-10)
IBUPOHIGHDOSE	0.32 (0.38)	9 (1-10)
IBUIVCONT	0.56 (0.43)	4 (1-10)
INDOIVCONT	0.29 (0.31)	9 (1-10)
INDOTHERS	0.45 (0.20)	6 (2-9)
PLAC_NORX	0.26 (0.15)	8 (4-10)

eFigure 12. Network meta-analysis forest plots for outcome: *Risk of Necrotizing Enterocolitis (NEC)*



eFigure 12. Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for risk of NEC computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

eTable 13. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of NEC

eTable 13. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of NEC

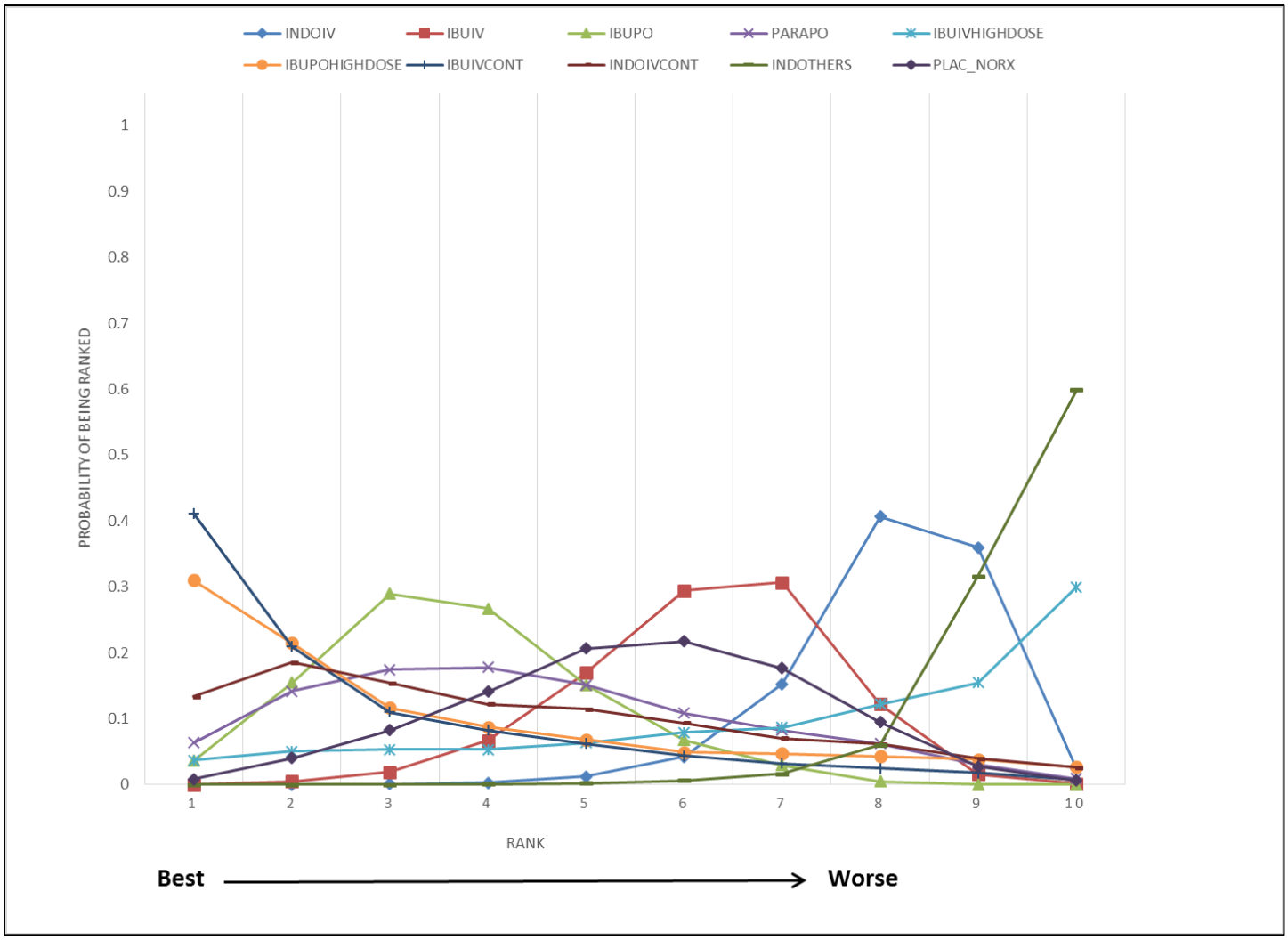
Treatment Comparison	No. of direct comparisons	Events in the intervention group (n/N)	Events in the comparison group (n/N)	Direct OR (95% CrI)	QoE (GRADE) based on direct comparisons	QoE (GRADE) based on indirect comparisons	Network OR (95% CrI)	Inconsistency assessment (based on node splitting p value)	Changes in GRADE assessment based on precision & effect size	Network QoE	Network absolute risk difference per 1000 infants (95% CrI)
versus INDOIV			(INDOIV)								ACR INDOIV 86/931 (9.2%)
IBUIV	10	22/417	29/404	0.73(0.39-1.41)	MODERATE	MODERATE	0.67(0.40-1.14)	0.64	None	MODERATE	29 fewer (from 12 more to 53 fewer)
IBUPO	4	8/52	14/51	0.38(0.11-1.29)	LOW	MODERATE	0.41(0.21-0.75)	0.69	None	MODERATE	52 fewer (from 21 fewer to 71 fewer)
PARAPO	1	2/38	4/39	0.43(0.04-2.98)	MODERATE	LOW	0.46(0.16-1.29)	0.6	None	MODERATE	48 fewer (from 24 more to 76 fewer)
IBUIVHIGHDOSE	———			———	———	MODERATE	0.97(0.17-6.29)	———	None	MODERATE	3 fewer (from 75 fewer to 298 more)
IBUPOHIGHDOSE	———			———	———	LOW	0.30(0.05-1.72)	———	Rated down (imprecision)	VERY LOW	63 fewer (from 57 more to 87 fewer)
IBUIVCONT	———			———	———	LOW	0.25(0.04-1.21)	———	Rated down (imprecision)	VERY LOW	68 fewer (from 17 more to 88 fewer)
INDOIVCONT	1	0/18	1/14	0.00(0.00-0.08)	LOW	LOW	0.42(0.11-1.63)	0.01	Rated down (inconsistency)	VERY LOW	51 fewer (from 50 more to 81 fewer)
INDOTHERS	6	40/300	30/296	1.40(0.76-2.62)	LOW	MODERATE	1.54(0.89-2.65)	0.58	None	MODERATE	43 more (from 9 fewer to 120 more)
PLAC_NORX	4	6/129	8/127	0.71(0.21-2.66)	MODERATE	MODERATE	0.60(0.29-1.21)	0.71	None	MODERATE	35 fewer (from 17 more to 64 fewer)
versus IBUIV			(IBUIV)								ACR IBUIV 64/778 (8.2%)
IBUPO	3	8/120	9/116	0.85(0.27-2.46)	HIGH	LOW	0.61(0.30-1.16)	0.89	None	HIGH	30 fewer (from 12 more to 56 fewer)
PARAPO	———			———	———	MODERATE	0.68(0.23-2.04)	———	None	MODERATE	25 fewer (from 62 fewer to 72 more)
IBUIVHIGHDOSE	1	4/35	3/35	1.47(0.24-11.01)	MODERATE	Not estimable	1.46(0.27-8.94)	NA	None	MODERATE	33 more (from 59 fewer to 363 more)
IBUPOHIGHDOSE	———			———	———	MODERATE	0.45(0.08-2.65)	———	Rated down (imprecision)	LOW	43 fewer (from 75 fewer to 110 more)
IBUIVCONT	1	3/55	7/56	0.36(0.06-1.99)	LOW	Not estimable	0.37(0.06-1.66)	NA	Rated down (imprecision)	VERY LOW	50 fewer (from 47 more to 77 fewer)
INDOIVCONT	1	7/31	9/32	0.71(0.18-2.77)	LOW	Not estimable	0.63(0.17-2.22)	0.21	None	LOW	29 fewer (from 67 fewer to 84 more)
INDOTHERS	———			———	———	LOW	2.30(1.10-4.81)	———	None	LOW	89 more (from 7 more to 219 more)
PLAC_NORX	2	11/119	14/122	0.73(0.26-2.02)	MODERATE	MODERATE	0.88(0.42-1.82)	0.75	None	MODERATE	9 fewer (from 46 fewer to 58 more)
versus IBUPO			(IBUPO)								ACR IBUPO 36/537 (6.7%)
PARAPO	3	10/164	9/163	1.10(0.39-3.34)	MODERATE	LOW	1.12(0.42-2.88)	0.7	None	MODERATE	7 more (from 38 fewer to 104 more)
IBUIVHIGHDOSE	———			———	———	MODERATE	2.39(0.38-16.16)	———	Rated down (imprecision)	LOW	80 more (from 40 fewer to 470 more)
IBUPOHIGHDOSE	1	4/30	5/30	0.75(0.14-3.79)	MODERATE	Not estimable	0.75(0.15-3.72)	NA	None	MODERATE	16 fewer (from 56 fewer to 144 more)
IBUIVCONT	———			———	———	LOW	0.62(0.09-3.15)	———	Rated down (imprecision)	VERY LOW	24 fewer (from 61 fewer to 118 more)
INDOIVCONT	———			———	———	LOW	1.02(0.25-4.43)	———	None	LOW	1 more (from 49 fewer to 174 more)
INDOTHERS	3	8/63	2/76	5.55(1.20-41.14)	LOW	Very low	3.77(1.77-8.47)	0.67	None	LOW	146 more (from 46 more to 311 more)
PLAC_NORX	3	7/96	4/96	1.99(0.50-9.54)	VERY LOW	LOW	1.46(0.66-3.36)	0.76	None	LOW	28 more (from 22 fewer to 127 more)
versus PARAPO			(PARAPO)								ACR PARAPO 12/202 (5.9%)
IBUIVHIGHDOSE	———			———	———	MODERATE	2.16(0.29-18.21)	———	Rated down (imprecision)	LOW	61 more (from 41 fewer to 476 more)
IBUPOHIGHDOSE	———			———	———	LOW	0.66(0.10-4.24)	———	None	LOW	19 fewer (from 53 fewer to 152 more)
IBUIVCONT	———			———	———	LOW	0.56(0.07-3.34)	———	Rated down (imprecision)	VERY LOW	25 fewer (from 55 fewer to 115 more)
INDOIVCONT	———			———	———	LOW	0.93(0.17-4.90)	———	None	LOW	4 fewer (from 49 fewer to 177 more)
INDOTHERS	———			———	———	LOW	3.36(1.10-10.38)	———	Rated down (imprecision)	VERY LOW	116 more (from 6 more to 337 more)
PLAC_NORX	———			———	———	MODERATE	1.31(0.41-4.17)	———	None	MODERATE	17 more (from 34 fewer to 149 more)
versus IBUIVHIGHDOSE			(IBUIVHIGHDOSE)								ACR IBUIVHIGHDOSE 4/35 (11.4%)
IBUPOHIGHDOSE	———			———	———	MODERATE	0.31(0.02-3.63)	———	Rated down (imprecision)	LOW	76 fewer (from 112 fewer to 205 more)
IBUIVCONT	———			———	———	LOW	0.26(0.02-2.48)	———	Rated down (imprecision)	VERY LOW	82 fewer (from 112 fewer to 128 more)
INDOIVCONT	———			———	———	LOW	0.43(0.05-3.62)	———	Rated down (imprecision)	VERY LOW	62 fewer (from 108 fewer to 204 more)
INDOTHERS	———			———	———	LOW	1.59(0.23-10.27)	———	Rated down (imprecision)	VERY LOW	56 more (from 85 fewer to 456 more)
PLAC_NORX	———			———	———	MODERATE	0.62(0.08-3.77)	———	Rated down (imprecision)	LOW	40 fewer (from 104 fewer to 213 more)

eTable 13. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of NEC

Treatment Comparison	No. of direct comparisons	Events in the intervention group (n/N)	Events in the comparison group (n/N)	Direct OR (95% CrI)	QoE (GRADE) based on direct comparisons	QoE (GRADE) based on indirect comparisons	Network OR (95% CrI)	Inconsistency assessment (based on node splitting p value)	Changes in GRADE assessment based on precision & effect size	Network QoE	Network absolute risk difference per 1000 infants (95% CrI)
(…continued)											
versus IBUPOHIGHDOSE			(IBUPOHIGHDOSE)								ACR IBUPOHIGHDOSE 4/30 (13.3%)
IBUIVCONT	———			———	———	LOW	0.83(0.07-8.22)	———	Rated down (imprecision)	VERY LOW	20 fewer (from 123 fewer to 425 more)
INDOIVCONT	———			———	———	LOW	1.36(0.17-12.04)	———	Rated down (imprecision)	VERY LOW	40 more (from 108 fewer to 516 more)
INDOTHERS	———			———	———	LOW	5.06(0.85-31.10)	———	Rated down (imprecision)	VERY LOW	304 more (from 18 fewer to 694 more)
PLAC_NORX	———			———	———	LOW	1.93(0.32-12.39)	———	Rated down (imprecision)	VERY LOW	96 more (from 86 fewer to 523 more)
versus IBUIVCONT			(IBUIVCONT)								ACR IBUIVCONT 3/55 (5.5%)
INDOIVCONT	———			———	———	LOW	1.67(0.23-16.00)	———	Rated down (imprecision)	VERY LOW	33 more (from 41 fewer to 425 more)
INDOTHERS	———			———	———	LOW	6.18(1.15-42.37)	———	Rated up (large effect)	MODERATE	208 more (from 8 more to 655 more)
PLAC_NORX	———			———	———	LOW	2.36(0.47-16.10)	———	Rated down (imprecision)	VERY LOW	65 more (from 28 fewer to 427 more)
versus INDOIVCONT			(INDOIVCONT)								ACR INDOIVCONT 7/49 (14.3%)
INDOTHERS	———			———	———	LOW	3.68(0.84-15.96)	———	Rated down (imprecision)	VERY LOW	237 more (from 20 fewer to 584 more)
PLAC_NORX	———			———	———	LOW	1.43(0.33-6.03)	———	None	LOW	50 more (from 91 fewer to 358 more)
versus INDOTHERS			(INDOTHERS)								ACR INDOTHERS 49/387 (12.7%)
PLAC_NORX	1	0/23	1/24	0.00(0.00-.08)	HIGH	LOW	0.38(0.15-0.94)	0.28	None	HIGH	74 fewer (from 7 fewer to 105 fewer)

Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk

eFigure 13. Ranking probability (rankogram) of each treatment modality for risk of NEC

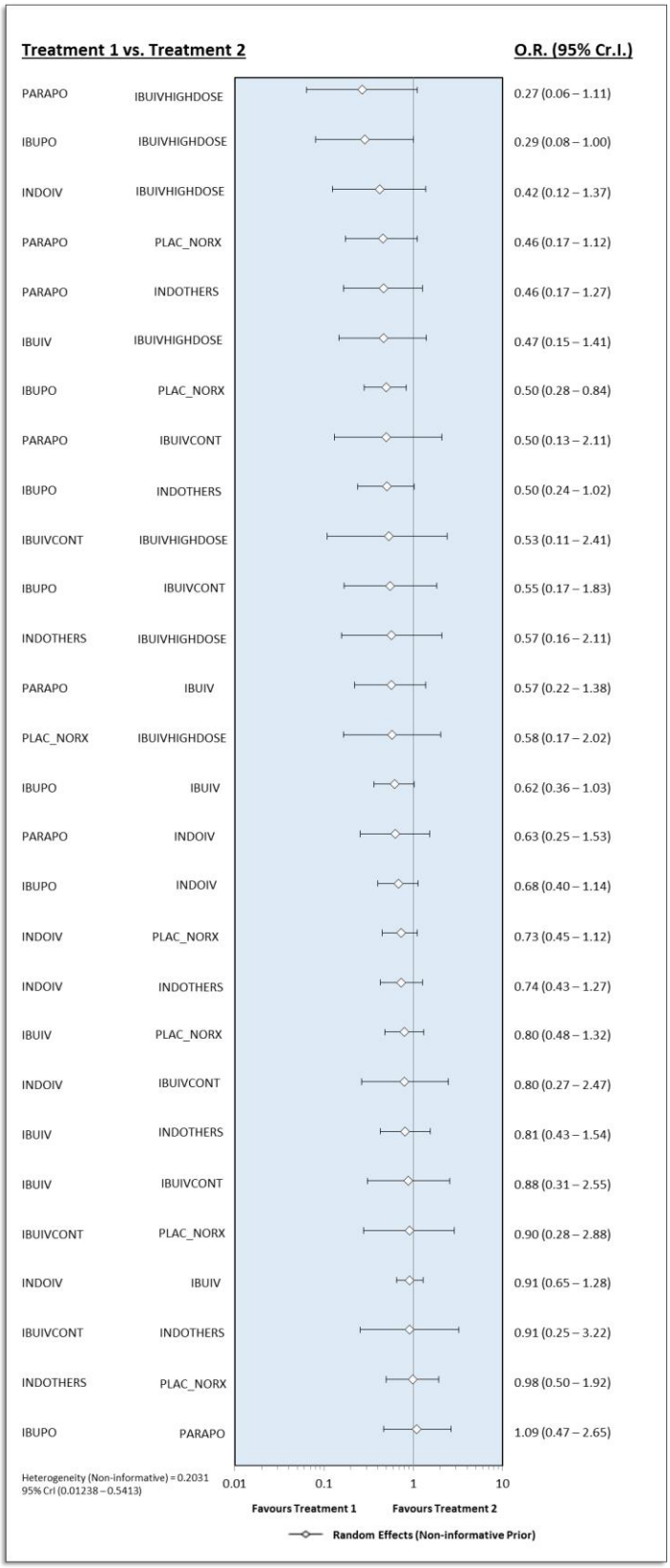


eFigure 13. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 10th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.

eTable 14. Ranking statistics for each treatment modality for risk of NEC

Risk of Necrotizing Enterocolitis		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95% Credible Intervals)**
INDOIV	0.21 (0.11)	8 (6-9)
IBUIV	0.42 (0.14)	6 (4-8)
IBUPO	0.70 (0.15)	4 (1-7)
PARAPO	0.62 (0.24)	4 (1-9)
IBUIVHIGHDOSE	0.30 (0.31)	8 (1-10)
IBUPOHIGHDOSE	0.74 (0.29)	2 (1-10)
IBUIVCONT	0.81 (0.24)	2 (1-9)
INDOIVCONT	0.65 (0.27)	4 (1-10)
INDOTHERS	0.06 (0.09)	10 (7-10)
PLAC_NORX	0.50 (0.19)	6 (2-9)

eFigure 14. Network meta-analysis forest plots for outcome: *Risk of Bronchopulmonary Dysplasia (BPD)*



eFigure 14. Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for risk of BPD computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

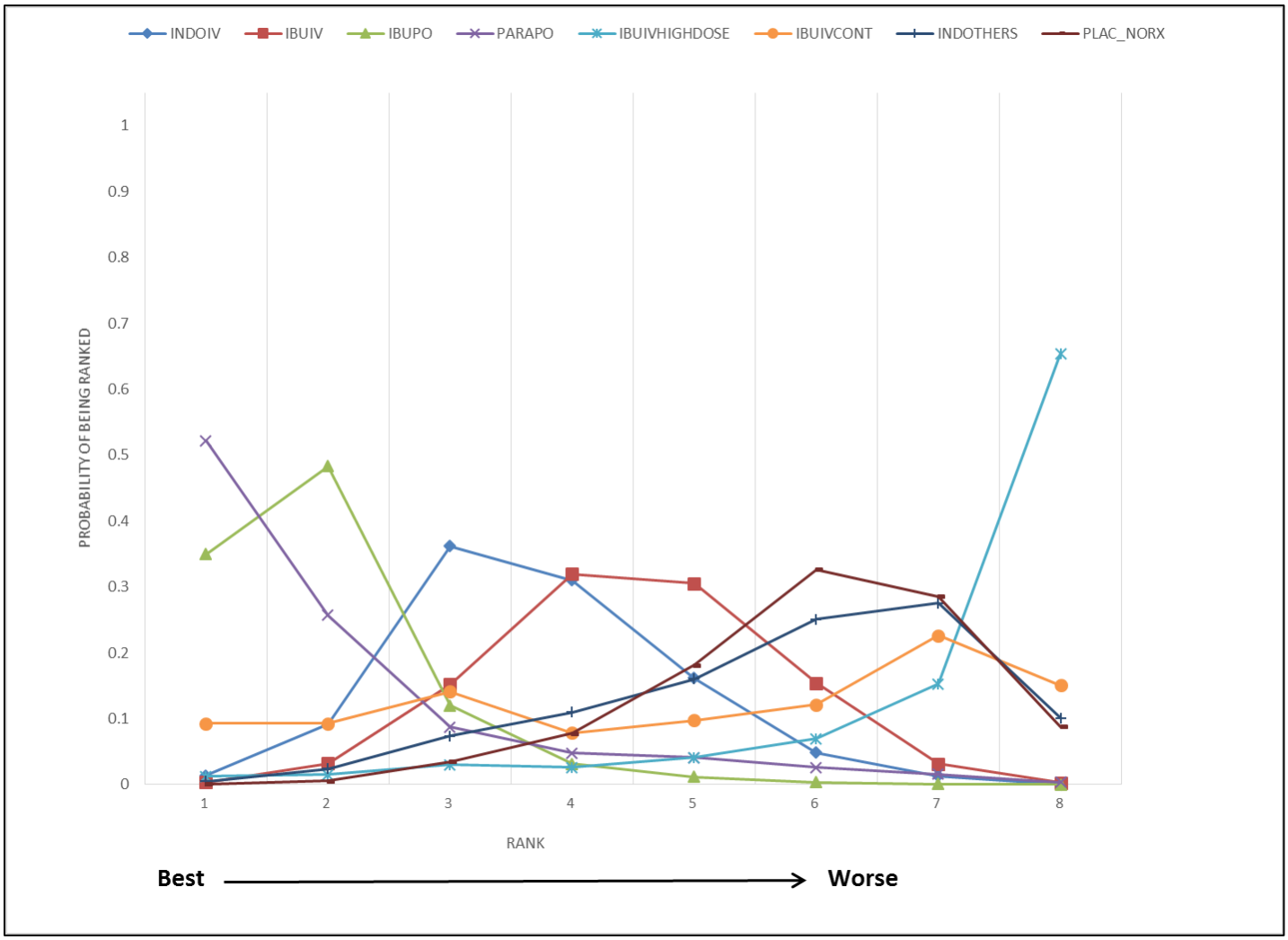
eTable 15. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of BPD

eTable 15. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of BPD

Treatment Comparison	No. of direct comparisons	Events in the intervention group (n/N)	Events in the comparison group(n/N)	Direct OR (95% CrI)	QoE (GRADE) based on direct comparisons	QoE (GRADE) based on indirect comparisons	Network OR (95% CrI)	Inconsistency assessment (based on node splitting p value)	Changes in GRADE assessment based on precision & effect size	Network QoE	Network absolute risk difference per 1000 infants (95% CrI)
versus INDOIV			(INDOIV)								ACR INDOIV 307/810 (37.9%)
IBUIV	8	152/392	143/385	1.10(0.73-1.61)	MODERATE	MODERATE	1.10(0.78-1.55)	0.41	None	MODERATE	23 more (from 56 fewer to 107 more)
IBUPO	2	12/24	13/24	0.80(0.23-2.92)	LOW	MODERATE	0.68(0.40-1.14)	0.65	None	MODERATE	86 fewer (from 31 more to 183 fewer)
PARAPO	1	5/38	6/39	0.82(0.18-3.60)	MODERATE	LOW	0.63(0.25-1.53)	0.81	None	MODERATE	101 fewer (from 104 more to 247 fewer)
IBUIVHIGHDOSE	———			———	———	MODERATE	2.37(0.73-8.02)	———	None	MODERATE	212 more (from 71 fewer to 451 more)
IBUIVCONT	———			———	———	LOW	1.25(0.40-3.76)	———	None	LOW	54 more (from 183 fewer to 317 more)
INDOTHERS	4	72/195	58/191	1.39(0.81-2.45)	LOW	MODERATE	1.36(0.78-2.32)	0.89	None	MODERATE	75 more (from 56 fewer to 207 more)
PLAC_NORX	5	95/175	87/171	1.30(0.75-2.34)	MODERATE	MODERATE	1.37(0.89-2.20)	0.58	None	MODERATE	76 more (from 27 fewer to 194 more)
versus IBUIV			(IBUIV)								ACR IBUIV 226/653 (34.6%)
IBUPO	3	30/120	35/116	0.72(0.34-1.48)	HIGH	LOW	0.62(0.36-1.03)	0.55	None	HIGH	99 fewer (from 7 more to 186 fewer)
PARAPO	———			———	———	MODERATE	0.57(0.22-1.38)	———	None	MODERATE	114 fewer (from 76 more to 242 fewer)
IBUIVHIGHDOSE	1	16/35	10/35	2.06(0.65-6.62)	MODERATE	NOT ESTIMABLE	2.14(0.71-6.86)	NA	None	MODERATE	185 more (from 73 fewer to 438 more)
IBUIVCONT	1	13/55	12/56	1.12(0.39-3.39)	LOW	NOT ESTIMABLE	1.13(0.39-3.26)	NA	None	LOW	28 more (from 175 fewer to 287 more)
INDOTHERS	———			———	———	LOW	1.23(0.65-2.35)	———	None	LOW	48 more (from 90 fewer to 208 more)
PLAC_NORX	1	16/51	17/54	1.00(0.36-2.75)	MODERATE	MODERATE	1.25(0.76-2.09)	0.4	None	MODERATE	52 more (from 59 fewer to 179 more)
versus IBUPO			(IBUPO)								ACR IBUPO 72/363 (19.8%)
PARAPO	2	9/124	11/123	0.79(0.25-2.51)	MODERATE	LOW	0.92(0.38-2.15)	0.85	None	MODERATE	13 fewer (from 112 fewer to 149 more)
IBUIVHIGHDOSE	———			———	———	MODERATE	3.49(1.00-12.43)	———	None	MODERATE	265 more (from 0 fewer to 556 more)
IBUIVCONT	———			———	———	LOW	1.82(0.55-5.91)	———	None	LOW	112 more (from 79 fewer to 396 more)
INDOTHERS	———			———	———	VERY LOW	1.99(0.98-4.16)	———	None	VERY LOW	132 more (from 3 fewer to 309 more)
PLAC_NORX	3	35/96	19/96	2.96(1.29-7.05)	VERY LOW	LOW	2.01(1.19-3.56)	0.32	None	LOW	134 more (from 29 more to 270 more)
versus PARAPO			(PARAPO)								ACR PARAPO 14/162 (8.6%)
IBUIVHIGHDOSE	———			———	———	MODERATE	3.74(0.90-15.61)	———	Rated down (imprecision)	LOW	175 more (from 8 fewer to 510 more)
IBUIVCONT	———			———	———	LOW	2.01(0.47-7.68)	———	None	LOW	73 more (from 44 fewer to 334 more)
INDOTHERS	———			———	———	LOW	2.16(0.79-6.01)	———	None	LOW	83 more (from 17 fewer to 276 more)
PLAC_NORX	———			———	———	MODERATE	2.17(0.89-5.76)	———	None	MODERATE	84 more (from 9 fewer to 266 more)
versus IBUIVHIGHDOSE			(IBUIVHIGHDOSE)								ACR IBUIVHIGHDOSE 16/35 (45.7%)
IBUIVCONT	———			———	———	LOW	0.53(0.11-2.41)	———	None	LOW	149 fewer (from 213 more to 372 fewer)
INDOTHERS	———			———	———	LOW	0.57(0.16-2.11)	———	None	LOW	133 fewer (from 183 more to 338 fewer)
PLAC_NORX	———			———	———	MODERATE	0.58(0.17-2.02)	———	None	MODERATE	129 fewer (from 173 more to 332 fewer)
versus IBUIVCONT			(IBUIVCONT)								ACR IBUIVCONT 13/55 (23.6%)
INDOTHERS	———			———	———	LOW	1.10(0.31-3.93)	———	None	LOW	18 more (from 149 fewer to 312 more)
PLAC_NORX	———			———	———	LOW	1.11(0.35-3.63)	———	None	LOW	19 more (from 139 fewer to 293 more)
versus INDOTHERS			(INDOTHERS)								ACR INDOTHERS 73/207 (35.3%)
PLAC_NORX	1	1/11	1/12	0.99(0.02-71.31)	HIGH	LOW	1.02(0.52-2.00)	0.21	None	HIGH	5 more (from 132 fewer to 169 more)

Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk

eFigure 15. Ranking probability (rankogram) of each treatment modality for risk of BPD

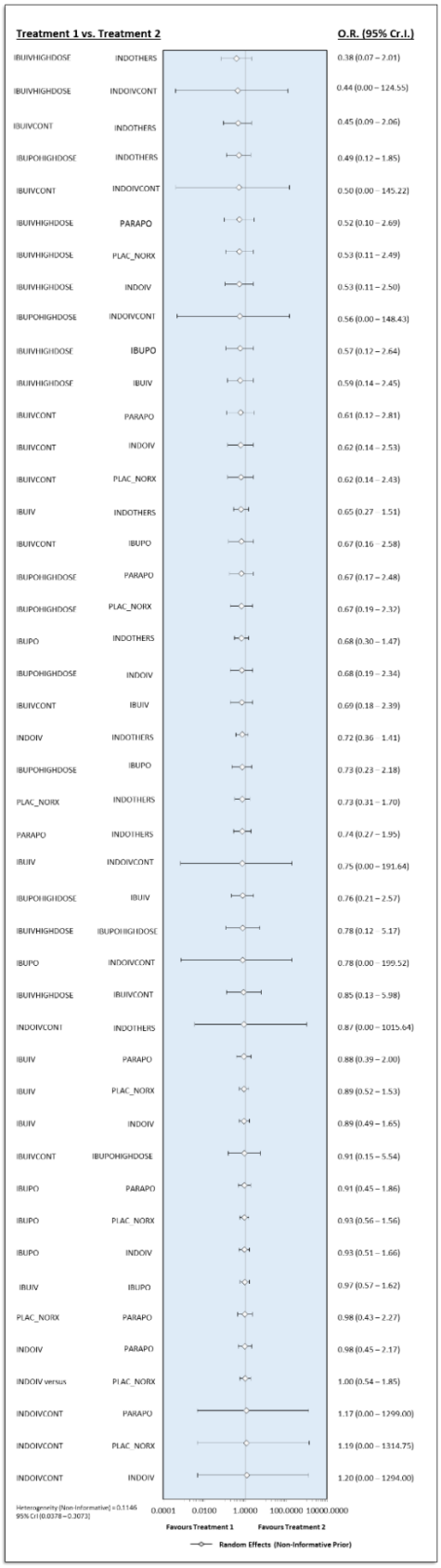


eFigure 15. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 8th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.

eTable 16. Ranking statistics for each treatment modality for risk of BPD

Risk of Bronchopulmonary Dysplasia		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95 % Credible Intervals)**
INDOIV	0.61 (0.16)	4 (2-6)
IBUIV	0.50 (0.16)	4 (2-7)
IBUPO	0.87 (0.13)	2 (1-4)
PARAPO	0.86 (0.21)	1 (1-6)
IBUIVHIGHDOSE	0.12 (0.22)	8 (2-8)
IBUIVCONT	0.43 (0.33)	5 (1-8)
INDOTHERS	0.32 (0.22)	6 (2-8)
PLAC_NORX	0.29 (0.18)	6 (3-8)

eFigure 16. Network meta-analysis forest plots for outcome: *Risk of Intraventricular Hemorrhage (IVH)*



eFigure 16. Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for risk of IVH computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

eTable 17. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of IVH

eTable 17. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of IVH											
Treatment Comparison	No. of direct comparisons	Events in the intervention group (n/N)	Events in the control group (n/N)	Direct OR (95% CrI)	QoE (GRADE) based on direct comparisons	QoE (GRADE) based on indirect comparisons	Network OR (95% CrI)	Inconsistency assessment (based on node splitting p value)	Changes in GRADE assessment based on precision & effect size	Network QoE	Network absolute risk difference per 1000 (95% CrI) infants
versus INDOIV			(INDOIV)								ACR INDOIV 53/285 (18.6%)
IBUIV	3	11/74	13/75	0.84(0.32-2.15)	MODERATE	MODERATE	0.89(0.49-1.65)	0.8	None	MODERATE	17 fewer (from 85 fewer to 88 more)
IBUPO	2	6/31	3/33	2.62(0.57-15.12)	LOW	MODERATE	0.93(0.51-1.66)	0.18	None	MODERATE	11 fewer (from 82 fewer to 89 more)
PARAPO	1	8/38	7/39	1.21(0.32-4.61)	MODERATE	LOW	1.02(0.46-2.23)	0.64	None	MODERATE	3 more (from 91 fewer to 152 more)
IBUIVHIGHDOSE	———	———	———	———	———	MODERATE	0.53(0.11-2.50)	———	None	MODERATE	78 fewer (from 161 fewer to 178 more)
IBUPOHIGHDOSE	———	———	———	———	———	LOW	0.68(0.19-2.34)	———	None	LOW	52 fewer (from 144 fewer to 162 more)
IBUIVCONT	———	———	———	———	———	LOW	0.62(0.14-2.53)	———	None	LOW	62 fewer (from 155 fewer to 180 more)
INDOIVCONT	1	0/18	0/14	1.21(0.00-1562)	LOW	NOT ESTIMABLE	1.20(0.00-1294)	NA	Rated down (imprecision)	VERY LOW	29 more (from – to 811 more)*
INDOTHERS	2	20/77	16/77	1.38(0.59-3.63)	LOW	MODERATE	1.38(0.71-2.77)	0.92	None	MODERATE	54 more (from 46 fewer to 202 more)
PLAC_NORX	2	10/47	14/47	0.63(0.22-1.84)	MODERATE	MODERATE	1.00(0.54-1.85)	0.21	None	MODERATE	0 fewer (from 76 fewer to 111 more)
versus IBUIV			(IBUIV)								ACR IBUIV 72/349 (20.6%)
IBUPO	3	25/120	23/116	1.10(0.52-2.34)	HIGH	LOW	1.04(0.62-1.77)	0.83	None	HIGH	6 more (from 68 fewer to 109 more)
PARAPO	———	———	———	———	———	MODERATE	1.14(0.50-2.59)	———	None	MODERATE	22 more (from 91 fewer to 196 more)
IBUIVHIGHDOSE	1	4/35	6/35	0.60(0.13-2.73)	MODERATE	NOT ESTIMABLE	0.59(0.14-2.45)	NA	None	MODERATE	73 fewer (from 171 fewer to 183 more)
IBUPOHIGHDOSE	———	———	———	———	———	MODERATE	0.76(0.21-2.57)	———	None	MODERATE	41 fewer (from 155 fewer to 194 more)
IBUIVCONT	1	5/55	7/56	0.70(0.17-2.75)	LOW	NOT ESTIMABLE	0.69(0.18-2.39)	NA	None	LOW	54 fewer (from 162 fewer to 177 more)
INDOIVCONT	———	———	———	———	———	LOW	1.34(0.01-1413)	———	Rated down (imprecision)	VERY LOW	52 more (from 204 fewer to 791 more)
INDOTHERS	———	———	———	———	———	LOW	1.54(0.66-3.64)	———	None	LOW	80 more (from 60 fewer to 280 more)
PLAC_NORX	1	25/68	25/68	0.99(0.40-2.50)	MODERATE	MODERATE	1.12(0.65-1.94)	0.69	None	MODERATE	19 more (from 62 fewer to 129 more)
versus IBUPO			(IBUPO)								ACR IBUPO 90/430 (20.9%)
PARAPO	2	14/124	14/123	1.01(0.41-2.51)	MODERATE	LOW	1.09(0.54-2.22)	0.74	None	MODERATE	15 more (from 84 fewer to 161 more)
IBUIVHIGHDOSE	———	———	———	———	———	MODERATE	0.57(0.12-2.64)	———	None	MODERATE	78 fewer (from 179 fewer to 202 more)
IBUPOHIGHDOSE	1	9/30	11/30	0.74(0.21-2.58)	MODERATE	NOT ESTIMABLE	0.73(0.23-2.18)	NA	None	MODERATE	47 fewer (from 152 fewer to 157 more)
IBUIVCONT	———	———	———	———	———	LOW	0.67(0.16-2.58)	———	None	LOW	59 fewer (from 169 fewer to 196 more)
INDOIVCONT	———	———	———	———	———	LOW	1.28(0.01-1343)	———	Rated down (imprecision)	VERY LOW	44 more (from 207 fewer to 788 more)
INDOTHERS	2	8/29	6/30	1.55(0.38-6.17)	LOW	VERY LOW	1.47(0.68-3.36)	0.96	None	VERY LOW	71 more (from 57 fewer to 261 more)
PLAC_NORX	3	35/96	28/96	1.44(0.70-3.00)	VERY LOW	LOW	1.08(0.64-1.79)	0.25	None	LOW	13 more (from 64 fewer to 112 more)
versus PARAPO			(PARAPO)								ACR PARAPO 22/162 (13.6%)
IBUIVHIGHDOSE	———	———	———	———	———	MODERATE	0.52(0.10-2.69)	———	None	MODERATE	60 fewer (from 120 fewer to 161 more)
IBUPOHIGHDOSE	———	———	———	———	———	LOW	0.67(0.17-2.48)	———	None	LOW	41 fewer (from 110 fewer to 145 more)
IBUIVCONT	———	———	———	———	———	LOW	0.61(0.12-2.81)	———	None	LOW	48 fewer (from 117 fewer to 171 more)
INDOIVCONT	———	———	———	———	———	LOW	1.17(0.00-1299)	———	Rated down (imprecision)	VERY LOW	20 more (from – to 859 more)*
INDOTHERS	———	———	———	———	———	LOW	1.35(0.51-3.64)	———	None	LOW	39 more (from 62 fewer to 228 more)
PLAC_NORX	———	———	———	———	———	MODERATE	0.98(0.43-2.27)	———	None	MODERATE	2 fewer (from 73 fewer to 127 more)
versus IBUIVHIGHDOSE			(IBUIVHIGHDOSE)								ACR IBUIVHIGHDOSE 4/35 (11.4%)
IBUPOHIGHDOSE	———	———	———	———	———	MODERATE	1.29(0.19-8.48)	———	None	MODERATE	28 more (from 90 fewer to 408 more)
IBUIVCONT	———	———	———	———	———	LOW	1.17(0.17-8.00)	———	None	LOW	17 more (from 93 fewer to 394 more)
INDOIVCONT	———	———	———	———	———	LOW	2.29(0.01-2484)	———	Rated down (imprecision)	VERY LOW	114 more (from 113 fewer to 883 more)
INDOTHERS	———	———	———	———	———	LOW	2.61(0.50-14.24)	———	Rated down (imprecision)	VERY LOW	138 more (from 54 fewer to 533 more)
PLAC_NORX	———	———	———	———	———	MODERATE	1.90(0.40-9.17)	———	None	MODERATE	83 more (from 65 fewer to 428 more)

eTable 17. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of IVH

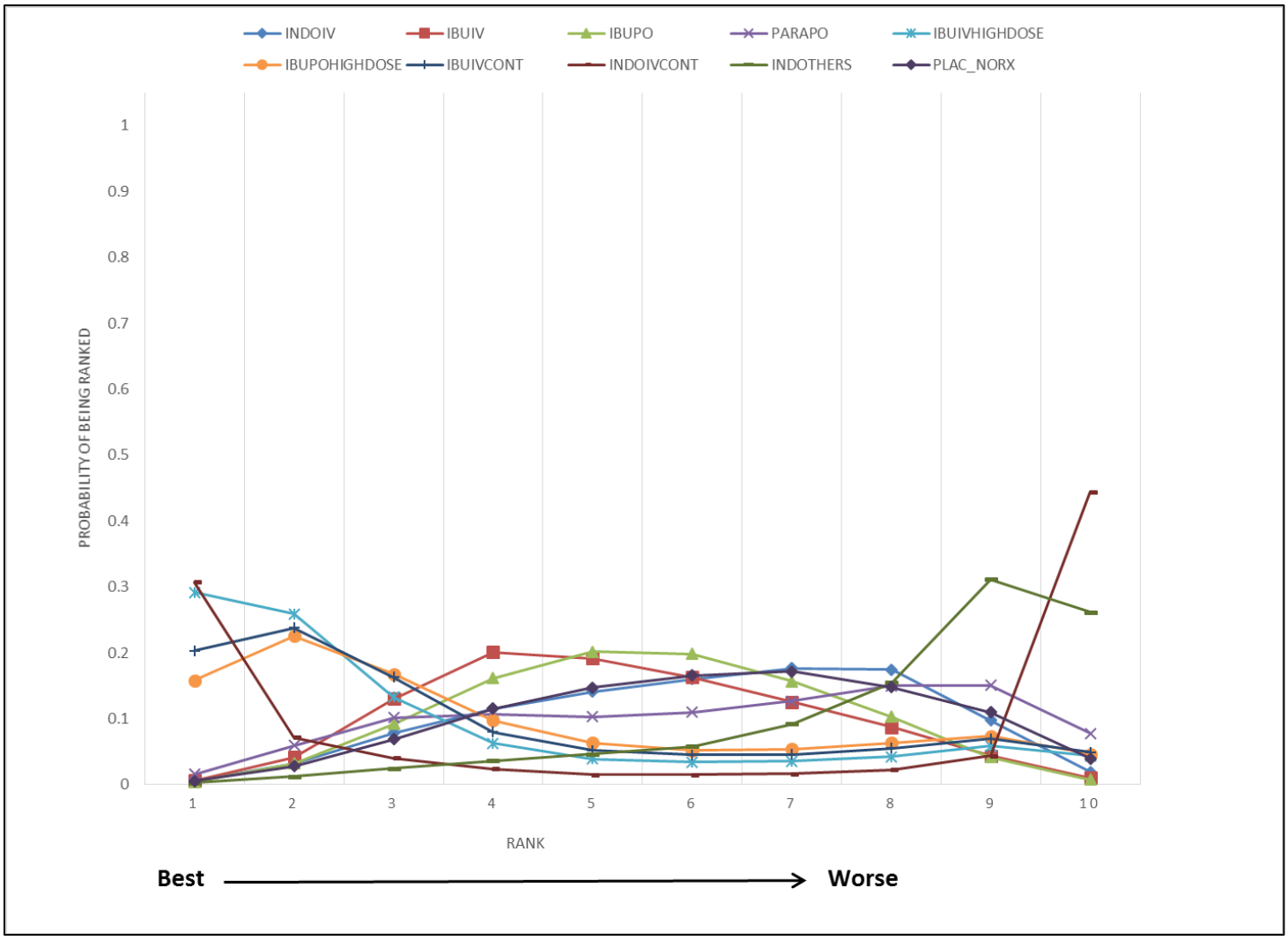
Treatment Comparison	No. of direct comparisons	Events in the intervention group (n/N)	Events in the control group (n/N)	Direct OR (95% CrI)	QoE (GRADE) based on direct comparisons	QoE (GRADE) based on indirect comparisons	Network OR (95% CrI)	Inconsistency assessment (based on node splitting p value)	Changes in GRADE assessment based on precision & effect size	Network QoE	Network absolute risk difference per 1000 (95% CrI) infants
(Continued……)											
versus IBUPOHIGHDOSE			(IBUPOHIGHDOSE)								ACR IBUPOHIGHDOSE 9/30 (30%)
IBUIVCONT	———	———	———	———	———	LOW	0.91(0.15-5.54)	———	None	LOW	19 fewer (from 240 fewer to 404 more)
INDOIVCONT	———	———	———	———	———	LOW	1.78(0.01-2077)	———	Rated down (imprecision)	VERY LOW	133 more (from 296 fewer to 699 more)
INDOTHERS	———	———	———	———	———	LOW	2.04(0.54-8.06)	———	None	LOW	166 more (from 112 fewer to 475 more)
PLAC_NORX	———	———	———	———	———	LOW	1.48(0.43-5.22)	———	None	LOW	88 more (from 144 fewer to 391 more)
versus IBUIVCONT			(IBUIVCONT)								ACR IBUIVCONT 5/55 (9.1%)
INDOIVCONT	———	———	———	———	———	LOW	1.99(0.01-2354)	———	Rated down (imprecision)	VERY LOW	75 more (from 90 fewer to 905 more)
INDOTHERS	———	———	———	———	———	LOW	2.24(0.48-11.08)	———	Rated down (imprecision)	VERY LOW	92 more (from 45 fewer to 435 more)
PLAC_NORX	———	———	———	———	———	LOW	1.61(0.41-6.95)	———	None	LOW	48 more (from 52 fewer to 319 more)
versus INDOIVCONT			(INDOIVCONT)								ACR INDOIVCONT 0/18 (0%) **
INDOTHERS	———	———	———	———	———	LOW	1.15(0.00-288)	———	Rated down (imprecision)	VERY LOW	4 more (from – to 864 more)*
PLAC_NORX	———	———	———	———	———	LOW	0.84(0.00-218)	———	Rated down (imprecision)	VERY LOW	4 fewer (from – to 834 more)*
versus INDOTHERS			(INDOTHERS)								ACR INDOTHERS 28/106 (26.4%)
PLAC_NORX	———	———	———	———	———	LOW	0.73(0.31-1.70)	———	None	LOW	57 fewer (from 115 more to 164 fewer)

Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk

*The lower limit of the 95% credible interval for absolute risk difference could not be computed due to the very low (tending to zero) lower limit of the 95% credible interval for the corresponding network odds ratio

**In view of zero event rate for the particular outcome in the control group, a continuity correction of 0.5 has been applied to calculate the assumed control risk in order to compute the absolute risk difference

eFigure 17. Ranking probability (rankogram) of each treatment modality for risk of IVH

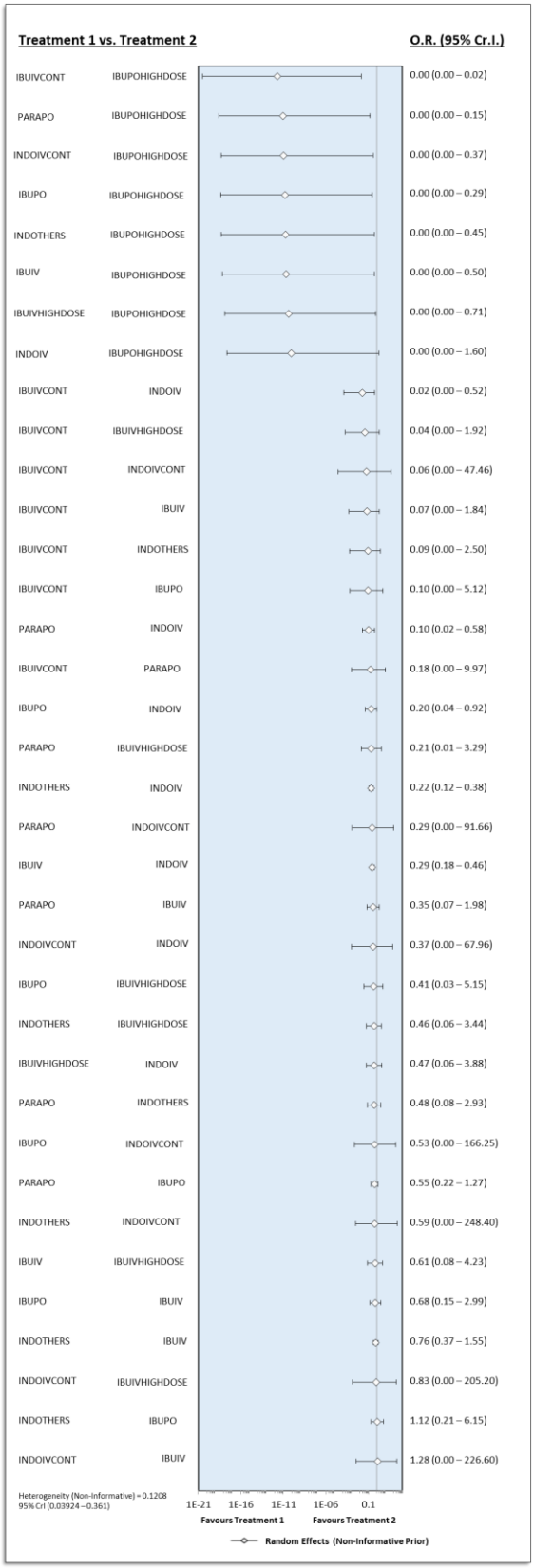


eFigure 17. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 10th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.

eTable 18. Ranking statistics for each treatment modality for risk of IVH

Risk of Intra-ventricular Hemorrhage		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95% Credible Intervals)**
INDOIV	0.43 (0.22)	6 (2-9)
IBUIV	0.52 (0.21)	5 (2-9)
IBUPO	0.49 (0.20)	6 (2-9)
PARAPO	0.42 (0.27)	7 (2-10)
IBUIVHIGHDOSE	0.73 (0.31)	2 (1-10)
IBUPOHIGHDOSE	0.65 (0.31)	3 (1-10)
IBUIVCONT	0.68 (0.31)	3 (1-10)
INDOIVCONT	0.45 (0.46)	8 (1-10)
INDOTHERS	0.21 (0.22)	9 (3-10)
PLAC_NORX	0.42 (0.23)	6 (2-10)

eFigure 18. Network meta-analysis forest plots for outcome: *Risk of Oliguria*



eFigure 18. Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for risk of oliguria computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

eTable 19. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of oliguria

eTable 19. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of oliguria											
Treatment Comparison	No. of direct comparisons	Events in the intervention group (n/N)	Events in the comparison group (n/N)	Direct OR (95% CrI)	QoE (GRADE) based on direct comparisons	QoE (GRADE) based on indirect comparisons	Network OR (95% CrI)	Inconsistency assessment (based on node splitting p value)	Changes in GRADE assessment based on precision & effect size	Network QoE	Network absolute risk difference per 1000 (95% CrI) infants
versus INDOIV			(INDOIV)								ACR INDOIV 143/734 (19.5%)
IBUIV	9	27/384	75/373	0.25(0.13-0.48)	MODERATE	MODERATE	0.29(0.18-0.46)	<0.01	High precision; network inconsistency ; no change in GRADE	MODERATE	129 fewer (from 95 fewer to 153 fewer)
IBUPO	———	———	———	———	LOW	MODERATE	0.20(0.04-0.92)	———	None	MODERATE	149 fewer (from 13 fewer to 185 fewer)
PARAPO	1	1/38	0/39	9.54E+17 (34.2-8.3E+40)	MODERATE	LOW	0.10(0.02-0.58)	<0.01	network inconsistency	VERY LOW	171 fewer (from 72 fewer to 190 fewer)
IBUIVHIGHDOSE	———	———	———	———	———	MODERATE	0.47(0.06-3.88)	———	Rated down (imprecision)	LOW	93 fewer (from 181 fewer to 289 more)
IBUPOHIGHDOSE	———	———	———	———	———	LOW	1.15E+10(0.62-4.34E+17)	———	Rated down (imprecision)	VERY LOW	805 more (from 64 fewer to 805 more)
IBUIVCONT	———	———	———	———	———	LOW	0.02(0.00-0.52)	———	None	LOW	190 fewer (up to 83 fewer)*
INDOIVCONT	———	———	———	———	———	LOW	0.37(0.00-67.96)	———	Rated down (imprecision)	VERY LOW	113 fewer (from – to 748 more)*
INDOTHERS	6	23/325	68/322	0.22 (0.10-0.44)	LOW	MODERATE	0.22(0.12-0.38)	0.8	Rated up (high precision; large effect)	HIGH	144 fewer (from 111 fewer to 167 fewer)
versus IBUIV			(IBUIV)								ACR IBUIV 34/655 (5.2%)
IBUPO	4	0/156	3/148	0.26(0.02-2.34)	HIGH	LOW	0.68(0.15-2.99)	<0.01	network inconsistency	VERY LOW	16 fewer (from 44 fewer to 89 more)
PARAPO	———	———	———	———	———	MODERATE	0.35(0.07-1.98)	———	Rated down (imprecision)	LOW	33 fewer (from 46 more to 48 fewer)
IBUIVHIGHDOSE	1	3/35	2/35	1.70(0.21-17.03)	MODERATE	NOT ESTIMABLE	1.64(0.24-11.85)	NA	Rated down (imprecision)	LOW	30 more (from 39 fewer to 342 more)
IBUPOHIGHDOSE	———	———	———	———	———	MODERATE	4.53E+10(1.99-1.37E+18)	———	Rated up (large effect)	HIGH	948 more (from 46 more to 948 more)
IBUIVCONT	1	0/55	2/56	0.10(0.00-3.43)	LOW	NOT ESTIMABLE	0.07(0.00-1.84)	NA	Rated down (imprecision)	VERY LOW	48 fewer (from – to 40 more)*
INDOIVCONT	1	0/31	0/32	0.92(0.00-246)	LOW	NOT ESTIMABLE	1.28(0.00-226.60)	NA	Rated down (imprecision)	VERY LOW	14 more (from – to 874 more)*
INDOTHERS	———	———	———	———	———	LOW	0.76(0.37-1.55)	———	None	LOW	12 fewer (from 26 more to 32 fewer)
versus IBUPO			(IBUPO)								ACR IBUPO 15/367 (4.1%)
PARAPO	3	7/164	15/163	0.42(0.12-1.21)	MODERATE	LOW	0.55(0.22-1.27)	<0.01	None	LOW	18 fewer (from 10 more to 32 fewer)
IBUIVHIGHDOSE	———	———	———	3.676642604	———	MODERATE	2.45(0.19-33.70)	———	Rated down (imprecision)	LOW	54 more (from 33 fewer to 549 more)
IBUPOHIGHDOSE	1	1/30	0/30	1.02E+14(178-6.59E+36)	MODERATE	NOT ESTIMABLE	5.71E+10(3.48-2.20E+18)	NA	Rated up (large effect)	HIGH	959 more (from 88 more to 959 more)
IBUIVCONT	———	———	———	———	———	LOW	0.10(0.00-5.12)	———	Rated down (imprecision)	VERY LOW	37 fewer (from – 138 more)*
INDOIVCONT	———	———	———	———	———	LOW	1.87(0.01-415.80)	———	Rated down (imprecision)	VERY LOW	33 more (from 40 fewer to 906 more)
INDOTHERS	1	0/18	0/18	0.78(0.00-303)	LOW	VERY LOW	1.12(0.21-6.15)	0.25	None	VERY LOW	5 more (from 32 fewer to 167 more)
versus PARAPO			(PARAPO)								ACR PARAPO 8/202 (4%)
IBUIVHIGHDOSE	———	———	———	———	———	MODERATE	4.71(0.30-71.49)	———	Rated down (imprecision)	LOW	123 more (from 27 fewer to 707 more)
IBUPOHIGHDOSE	———	———	———	———	———	LOW	1.12E+11(6.51-4.06E+18)	———	Rated up (large effect)	MODERATE	960 more (from 172 more to 960 more)
IBUIVCONT	———	———	———	———	———	LOW	0.18(0.00-9.97)	———	Rated down (imprecision)	VERY LOW	32 fewer (from – to 252 more)*
INDOIVCONT	———	———	———	———	———	LOW	3.43(0.01-866.40)	———	Rated down (imprecision)	VERY LOW	84 more (from 39 fewer to 933 more)
INDOTHERS	———	———	———	———	———	LOW	2.10(0.34-13.05)	———	Rated down (imprecision)	VERY LOW	40 more (from 26 fewer to 310 more)
versus IBUIVHIGHDOSE			(IBUIVHIGHDOSE)								ACR IBUIVHIGHDOSE 3/35 (8.6%)
IBUPOHIGHDOSE	———	———	———	———	———	MODERATE	2.43E+10(1.40-7.54E+17)	———	Rated up (large effect)	HIGH	914 more (from 30 more to 914 more)
IBUIVCONT	———	———	———	———	———	LOW	0.04(0.00-1.92)	———	Rated down (imprecision)	VERY LOW	82 fewer (from – to 67 more)*
INDOIVCONT	———	———	———	———	———	LOW	0.83(0.00-205.20)	———	Rated down (imprecision)	VERY LOW	14 fewer (from – to 865 more)*

eTable 19. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of oliguria

Treatment Comparison	No. of direct comparisons	Events in the intervention group (n/N)	Events in the comparison group (n/N)	Direct OR (95% CrI)	QoE (GRADE) based on direct comparisons	QoE (GRADE) based on indirect comparisons	Network OR (95% CrI)	Inconsistency assessment (based on node splitting p value)	Changes in GRADE assessment based on precision & effect size	Network QoE	Network absolute risk difference per 1000 (95% CrI) infants
											(Continued…..)
INDOTHERS	———	———	———	———	———	LOW	0.46(0.06-3.44)	———	Rated down (imprecision)	VERY LOW	44 fewer (from 80 fewer to 158 more)
versus IBUPOHIGHDOSE			(IBUPOHIGHDOSE)								ACR IBUPOHIGHDOSE 1/30 (3.3%)
IBUIVCONT	———	———	———	———	———	LOW	0.00(0.00-0.02)	———	Rated up (large effect)	MODERATE	-- (up to 33 fewer)***
INDOIVCONT	———	———	———	———	———	LOW	0.00(0.00-0.37)	———	Rated up (large effect)	MODERATE	-- (up to 21 fewer)***
INDOTHERS	———	———	———	———	———	LOW	0.00(0.00-0.45)	———	Rated up (large effect)	MODERATE	-- (up to 18 fewer)***
versus IBUIVCONT			(IBUIVCONT)								ACR IBUIVCONT 0/55 (0%) **
INDOIVCONT	———	———	———	———	———	LOW	17.44(0.02-36280.00)	———	Rated down (imprecision)	VERY LOW	129 more (from 9 fewer to 988 more)
INDOTHERS	———	———	———	———	———	LOW	11.13(0.40-1693.00)	———	Rated down (imprecision)	VERY LOW	84 more (from 5 fewer to 930 more)
versus INDOIVCONT			(INDOIVCONT)								ACR INDOIVCONT 0/31 (0%) **
INDOTHERS	———	———	———	———	———	LOW	0.59(0.00-248.40)	———	Rated down (imprecision)	VERY LOW	7 fewer (from – to 787 more)*

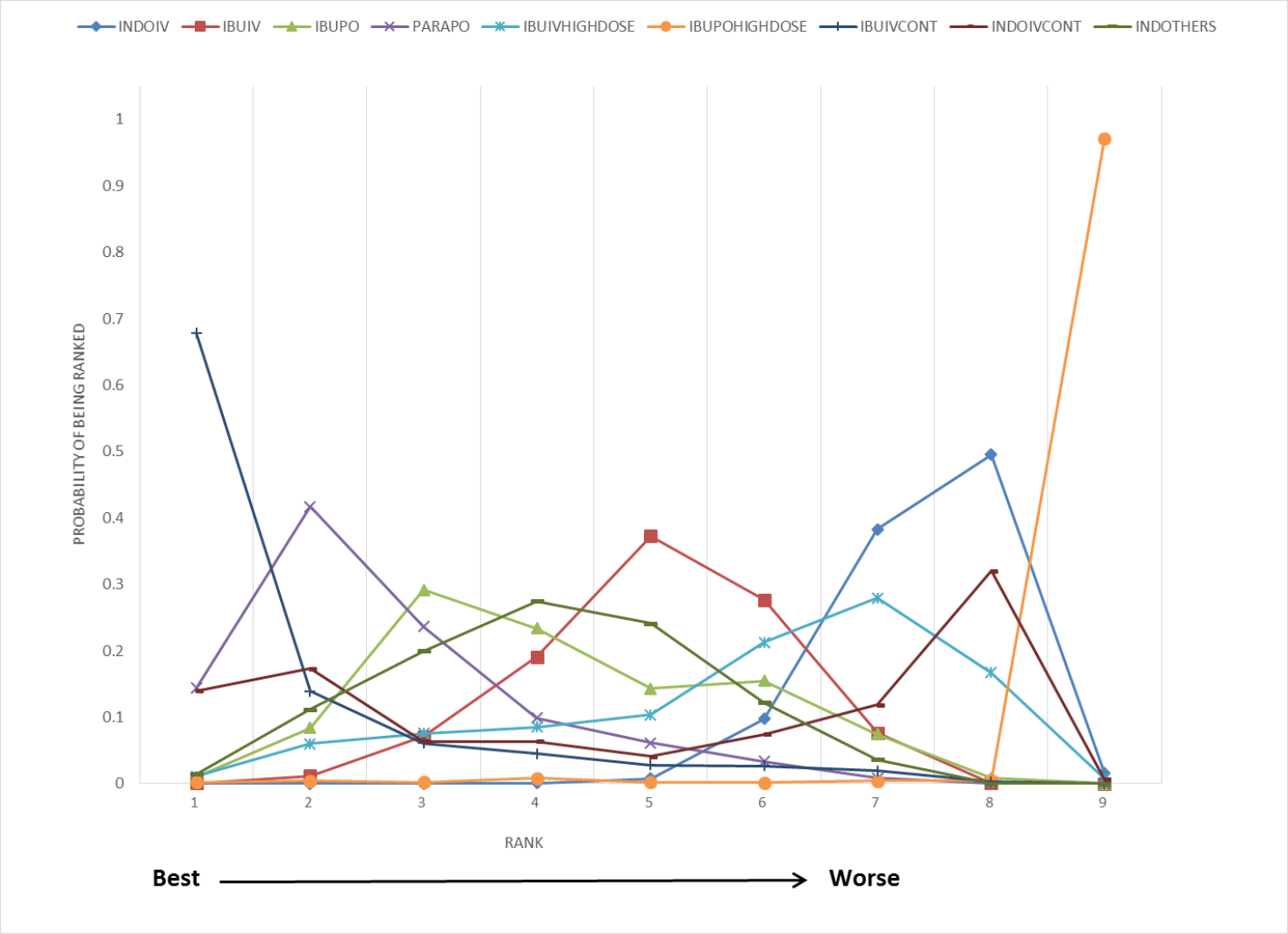
Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk

*The lower limit of the 95% credible interval for absolute risk difference could not be computed due to the very low (tending to zero) lower limit of the 95% credible interval for the corresponding network odds ratio

**In view of zero event rate for the particular outcome in the control group, a continuity correction of 0.5 has been applied to calculate the assumed control risk in order to compute the absolute risk difference

***The absolute risk difference could not be computed due to very low (tending to zero) network odds ratio

eFigure 19. Ranking probability (rankogram) of each treatment modality for risk of oliguria



eFigure 19. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 9th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.

eTable 20. Ranking statistics for each treatment modality for risk of oliguria

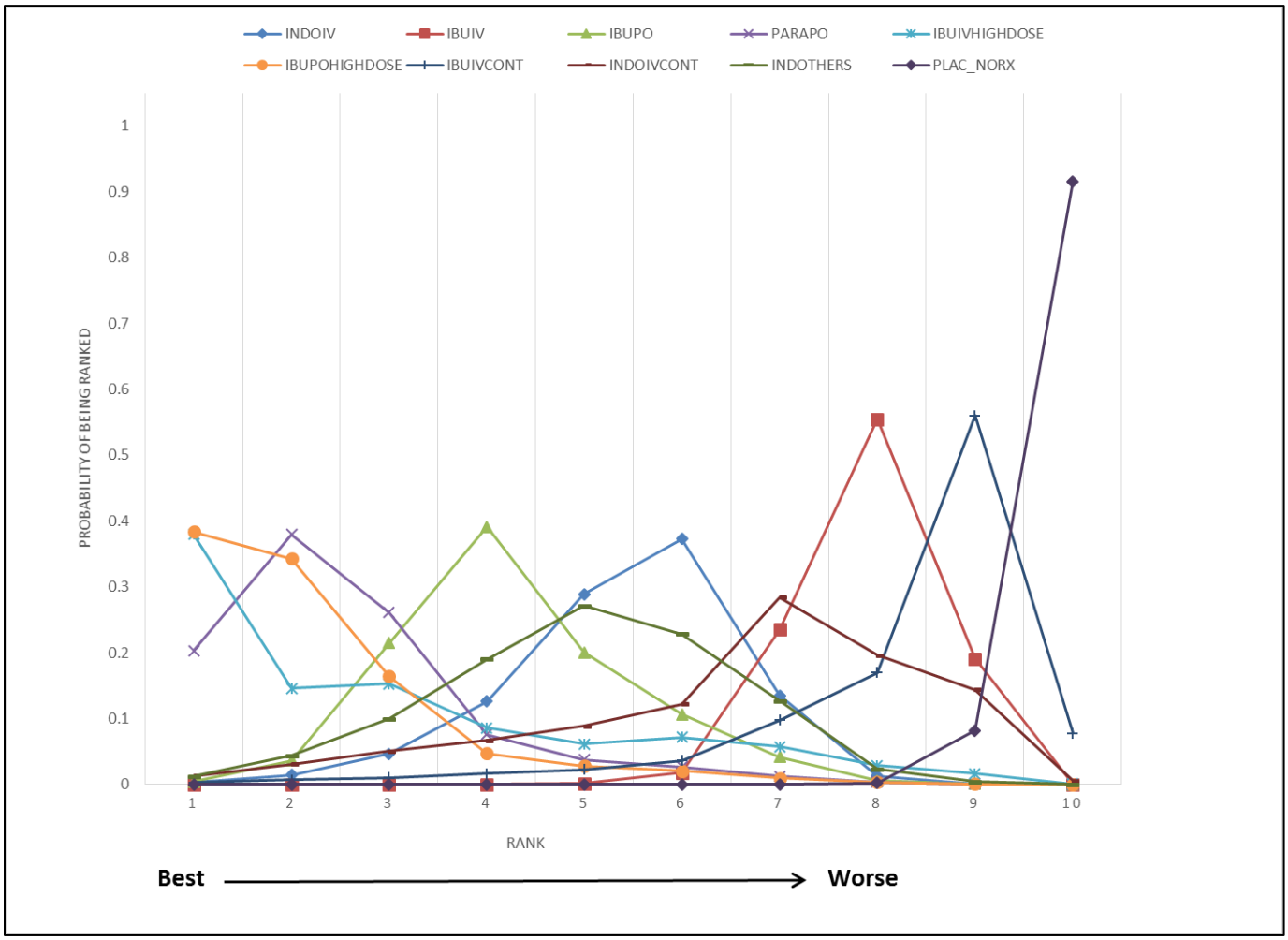
Risk of oliguria		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95% Credible Intervals)**
INDOIV	0.20 (0.09)	8 (6-8)
IBUIV	0.49 (0.14)	5 (3-7)
IBUPO	0.60 (0.19)	4 (2-7)
PARAPO	0.79 (0.16)	2 (1-6)
IBUIVHIGHDOSE	0.40 (0.23)	6 (2-8)
IBUPOHIGHDOSE	0.02 (0.10)	9 (8-9)
IBUIVCONT	0.90 (0.18)	1 (1-6)
INDOIVCONT	0.50 (0.35)	6 (1-8)
INDOTHERS	0.61 (0.17)	4 (2-7)

eTable 21. Network effect estimates for PDA closure on sensitivity analysis ('low' & 'probably low' risk of bias studies)

IBUPOHIGHDOSE									
1.15 (0.46 – 2.97)	PARAPO								
1.15 (0.17 – 7.55)	1.00 (0.16 – 6.24)	IBUIVHIGHDOSE							
1.81 (0.77 – 4.46)	1.58 (0.74 – 3.46)	1.58 (0.30 – 8.53)	IBUPO						
2.18 (0.70 – 6.49)	1.88 (0.67 – 5.03)	1.86 (0.34 – 10.23)	1.18 (0.57 – 2.36)	INDOTHERS					
2.33 (0.80 – 6.91)	2.02 (0.78 – 5.32)	2.01 (0.41 – 10.48)	1.28 (0.66 – 2.42)	1.08 (0.60 – 2.02)	INDOIV				
3.23 (0.75 – 14.95)	2.82 (0.70 – 12.03)	2.86 (0.43 – 19.72)	1.78 (0.54 – 6.23)	1.51 (0.45 – 5.44)	1.40 (0.47 – 4.33)	INDOIVCONT			
4.34 (1.52 – 12.78)	3.77 (1.47 – 10.04)	3.76 (0.83 – 18.23)	2.39 (1.30 – 4.49)	2.01 (1.04 – 4.12)	1.86 (1.19 – 3.01)	1.33 (0.44 – 3.92)	IBUIV		
6.00 (1.21 – 31.95)	5.18 (1.12 – 25.40)	5.21 (0.76 – 38.40)	3.32 (0.83 – 13.23)	2.77 (0.70 – 11.91)	2.59 (0.69 – 9.71)	1.86 (0.36 – 9.53)	1.39 (0.40 – 4.75)	IBUIVCONT	
15.85 (5.34 – 49.75)	13.82 (5.07 – 38.65)	13.78 (2.66 – 77.16)	8.72 (4.44 – 17.47)	7.36 (3.98 – 14.56)	6.82 (3.81 – 12.75)	4.88 (1.44 – 16.32)	3.67 (1.93 – 6.95)	2.63 (0.66 – 10.75)	PLAC_NORX

Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for PDA closure computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values

eFigure 20. Rankogram for PDA closure on sensitivity analysis ('low' & 'probably low' risk of bias studies)



eTable 22. Ranking statistics for PDA closure on sensitivity analysis ('low' & 'probably low' risk of bias studies)

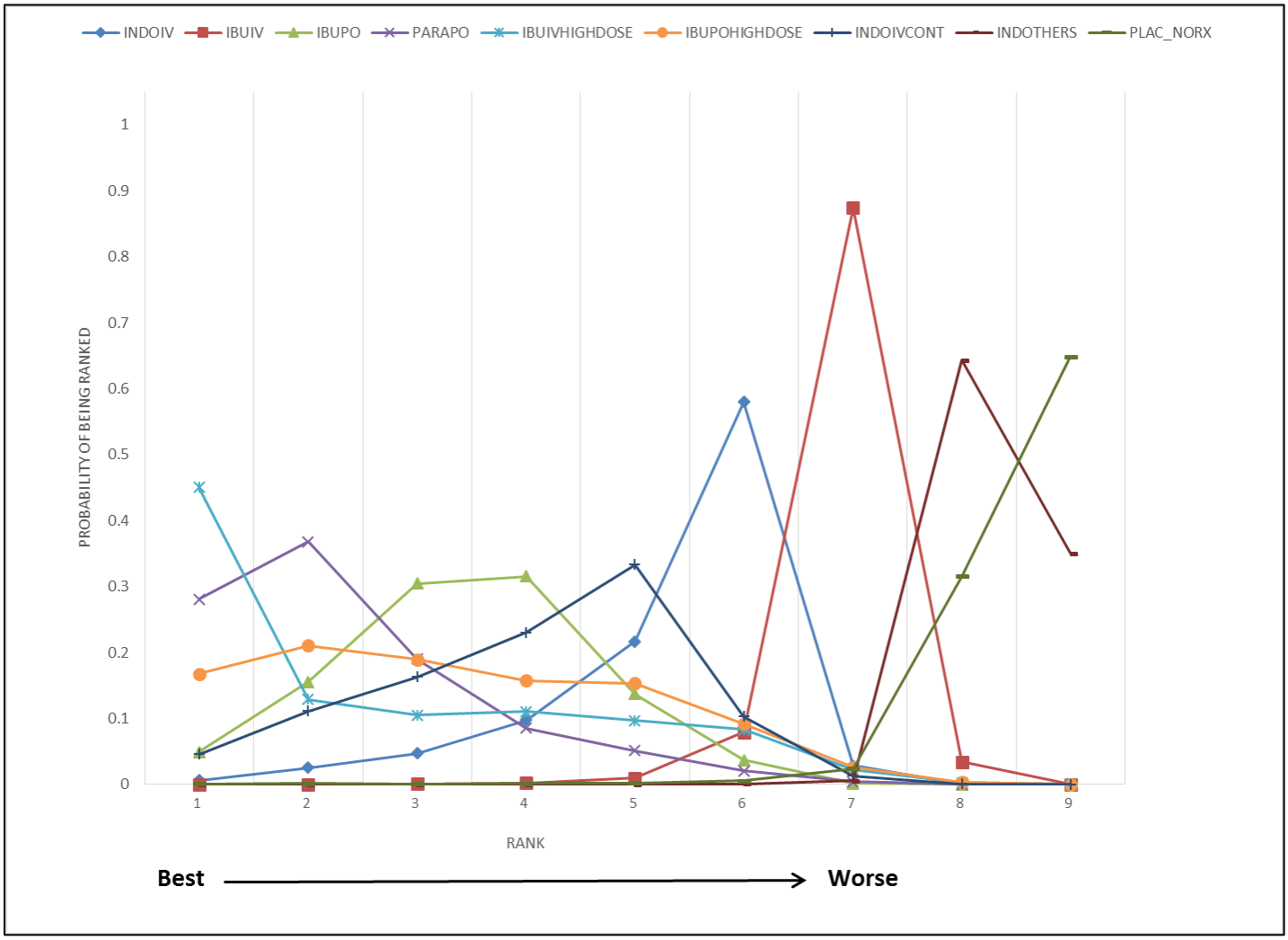
PDA closure		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95% Credible Intervals)**
INDOIV	0.51 (0.13)	6 (3-7)
IBUIV	0.23 (0.08)	8 (7-9)
IBUPO	0.64 (0.13)	4 (2-7)
PARAPO	0.83 (0.15)	2 (1-6)
IBUIVHIGHDOSE	0.78 (0.25)	2 (1-8)
IBUPOHIGHDOSE	0.88 (0.15)	2 (1-6)
IBUIVCONT	0.19 (0.16)	9 (4-10)
INDOIVCONT	0.38 (0.22)	7 (2-9)
INDOTHERS	0.56 (0.16)	5 (2-8)
PLAC_NORX	0.01 (0.03)	10 (9-10)

eTable 23. Network effect estimates for need for repeat pharmacotherapy on sensitivity analysis ('low' & 'probably low' risk of bias studies)

PARAPO								
1.05 (0.20 – 5.93)	**IBUIVHIGHDOSE**							
0.81 (0.34 – 2.04)	0.78 (0.12 – 4.71)	**IBUPOHIGHDOSE**						
0.77 (0.38 – 1.59)	0.74 (0.15 – 3.33)	0.95 (0.37 – 2.30)	**IBUPO**					
0.66 (0.22 – 1.74)	0.63 (0.12 – 2.77)	0.81 (0.23 – 2.48)	0.84 (0.38 – 1.81)	**INDOIVCONT**				
0.47 (0.17 – 1.34)	0.45 (0.09 – 1.92)	0.58 (0.17 – 1.90)	0.61 (0.27 – 1.38)	0.72 (0.35 – 1.58)	**INDOIV**			
0.28 (0.10 – 0.73)	0.27 (0.06 – 1.00)	0.34 (0.10 – 1.06)	0.36 (0.18 – 0.72)	0.43 (0.22 – 0.89)	0.60 (0.32 – 1.02)	**IBUIV**		
0.07 (0.02 – 0.28)	0.07 (0.01 – 0.37)	0.09 (0.02 – 0.37)	0.10 (0.04 – 0.29)	0.12 (0.05 – 0.31)	0.16 (0.06 – 0.45)	0.27 (0.11 – 0.68)	**INDOTHERS**	
0.05 (0.00 – 0.38)	0.05 (0.00 – 0.45)	0.06 (0.00 – 0.51)	0.07 (0.01 – 0.43)	0.08 (0.01 – 0.52)	0.11 (0.01 – 0.58)	0.18 (0.02 – 1.14)	0.67 (0.06 – 4.89)	**PLAC_NORX**

Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for need for repeat pharmacotherapy computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values

eFigure 21. Rankogram for need for repeat pharmacotherapy on sensitivity analysis ('low' & 'probably low' risk of bias studies)



eTable 24. Ranking statistics for need for repeat pharmacotherapy on sensitivity analysis ('low' & 'probably low' risk of bias studies)

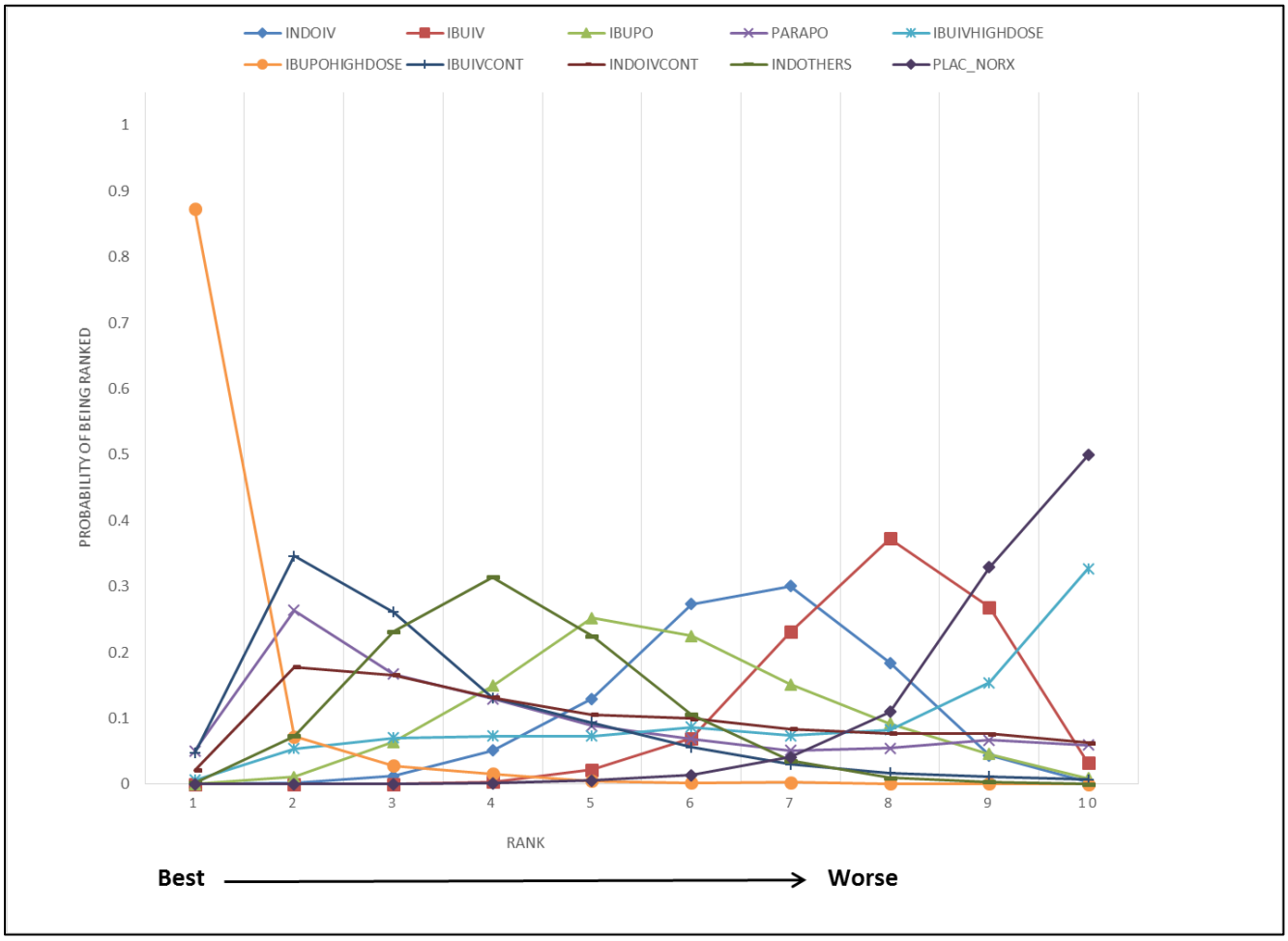
Need for repeat pharmacotherapy		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95% Credible Intervals)**
INDOIV	0.46 (0.14)	6 (2-7))
IBUIV	0.26 (0.05)	7 (6-8)
IBUPO	0.69 (0.15)	3 (1-6)
PARAPO	0.83 (0.16)	2 (1-5)
IBUIVHIGHDOSE	0.80 (0.23)	2 (1-7)
IBUPOHIGHDOSE	0.71 (0.21)	3 (1-7)
INDOIVCONT	0.62 (0.17)	4 (1-6)
INDOTHERS	0.08 (0.06)	8 (8-9)
PLAC_NORX	0.05 (0.09)	9 (7-9)

eTable 25. Network effect estimates for need for surgical PDA ligation on sensitivity analysis ('low' & 'probably low' risk of bias studies)

IBUPOHIGHDOSE									
0.05 (0.00 – 2.60)	IBUIVCONT								
0.03 (0.00 – 0.87)	0.57 (0.08 – 3.85)	INDOTHERS							
0.03 (0.00 – 2.95)	0.71 (0.03 – 16.93)	1.16 (0.10 – 18.05)	PARAPO						
0.02 (0.00 – 1.83)	0.54 (0.03 – 7.74)	0.89 (0.09 – 11.48)	0.72 (0.02 – 22.85)	INDOIVCONT					
0.02 (0.00 – 0.47)	0.38 (0.04 – 2.59)	0.65 (0.21 – 1.90)	0.56 (0.04 – 5.50)	0.75 (0.05 – 7.10)	IBUPO				
0.01 (0.00 – 0.44)	0.29 (0.05 – 1.80)	0.50 (0.21 – 1.31)	0.42 (0.03 – 5.19)	0.56 (0.05 – 4.98)	0.77 (0.26 – 2.51)	INDOIV			
0.01 (0.00 – 0.61)	0.20 (0.01 – 4.09)	0.35 (0.03 – 4.77)	0.31 (0.01 – 9.35)	0.40 (0.01 – 9.22)	0.54 (0.04 – 7.59)	0.70 (0.06 – 8.19)	IBUIVHIGHDOSE		
0.01 (0.00 – 0.33)	0.22 (0.03 – 1.07)	0.37 (0.14 – 0.92)	0.30 (0.02 – 3.64)	0.42 (0.04 – 3.15)	0.57 (0.19 – 1.66)	0.75 (0.35 – 1.27)	1.08 (0.09 – 10.90)	IBUIV	
0.01 (0.00 – 0.24)	0.13 (0.02 – 0.82)	0.22 (0.10 – 0.48)	0.18 (0.01 – 2.49)	0.24 (0.02 – 2.28)	0.34 (0.10 – 1.10)	0.43 (0.17 – 1.01)	0.62 (0.05 – 7.72)	0.59 (0.24 – 1.52)	PLAC_NORX

Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for need for surgical PDA ligation computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values

eFigure 22. Rankogram for need for surgical PDA ligation on sensitivity analysis ('low' & 'probably low' risk of bias studies)



eTable 26. Ranking statistics for need for surgical PDA ligation on sensitivity analysis ('low' & 'probably low' risk of bias studies)

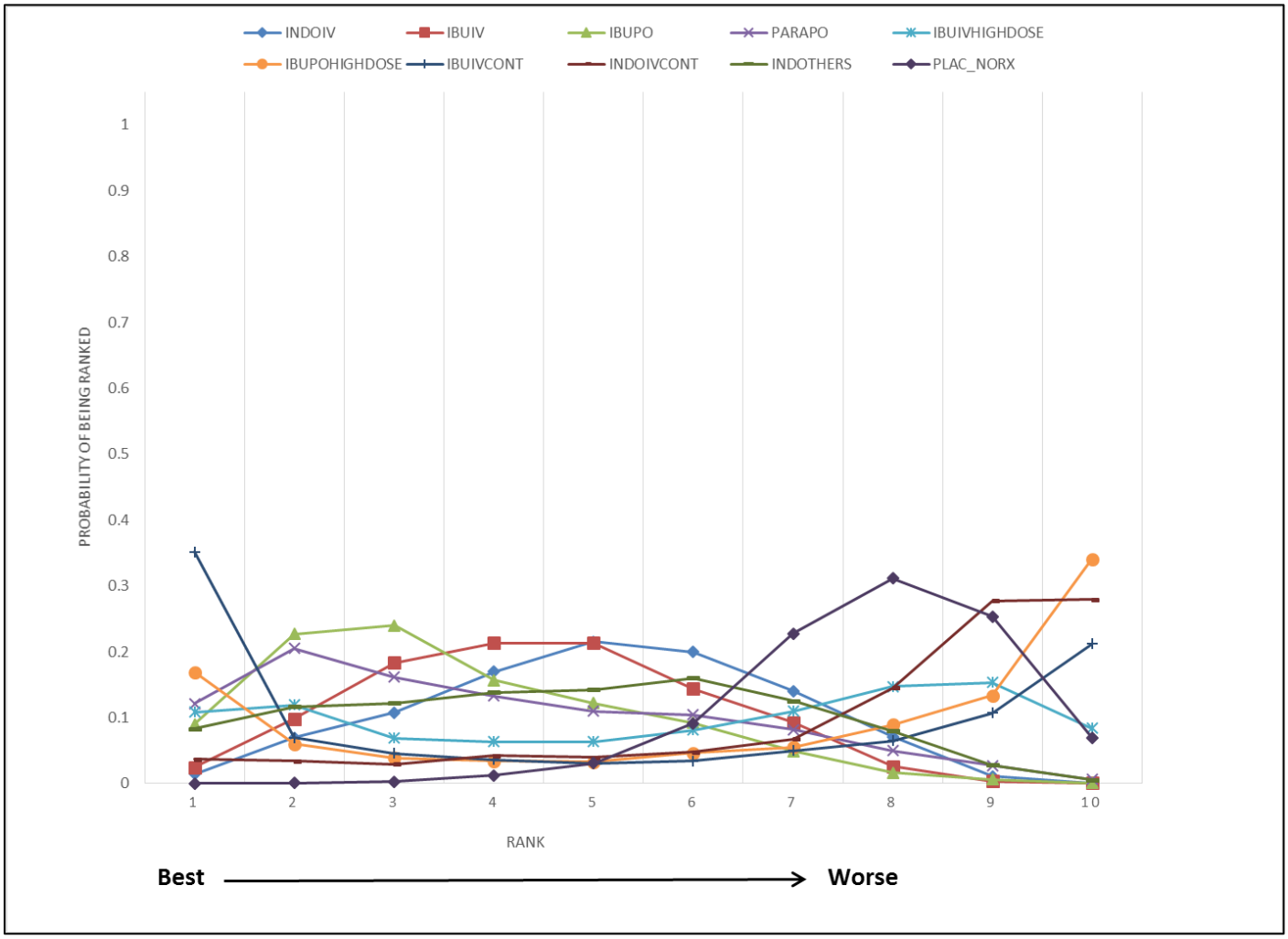
Need for surgical PDA ligation		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95% Credible intervals)**
INDOIV	0.39 (0.14)	7 (4-9)
IBUIV	0.24 (0.12)	8 (5-10)
IBUPO	0.48 (0.18)	6 (3-9)
PARAPO	0.62 (0.29)	4 (1-10)
IBUIVHIGHDOSE	0.30 (0.30)	8 (2-10)
IBUPOHIGHDOSE	0.97 (0.09)	1 (1-4)
IBUIVCONT	0.74 (0.19)	3 (1-8)
INDOIVCONT	0.55 (0.29)	5 (2-10)
INDOTHERS	0.64 (0.14)	4 (2-7)
PLAC_NORX	0.08 (0.11)	9 (7-10)

eTable 27. Network effect estimates for neonatal mortality on sensitivity analysis ('low' & 'probably low' risk of bias studies)

IBUPO									
0.96 (0.41 – 2.07)	**PARAPO**								
0.85 (0.41 – 1.81)	0.90 (0.35 – 2.32)	**IBUIV**							
0.83 (0.33 – 2.25)	0.85 (0.30 – 2.68)	0.97 (0.42 – 2.19)	**INDOTHERS**						
0.86 (0.01 – 27.31)	0.87 (0.02 – 29.74)	1.00 (0.02 – 30.42)	1.02 (0.02 – 33.02)	**IBUIVCONT**					
0.78 (0.36 – 1.76)	0.82 (0.33 – 2.04)	0.91 (0.50 – 1.70)	0.94 (0.46 – 2.03)	0.92 (0.03 – 64.11)	**INDOIV**				
0.66 (0.12 – 3.32)	0.69 (0.12 – 3.94)	0.77 (0.18 – 3.27)	0.81 (0.14 – 4.48)	0.80 (0.02 – 41.76)	0.84 (0.17 – 4.06)	**IBUIVHIGHDOSE**			
0.42 (0.01 – 5.24)	0.45 (0.02 – 6.09)	0.51 (0.02 – 7.33)	0.49 (0.02 – 7.70)	0.40 (0.00 – 85.48)	0.54 (0.02 – 7.83)	0.62 (0.02 – 13.66)	**IBUPOHIGHDOSE**		
0.36 (0.05 – 1.96)	0.39 (0.04 – 2.33)	0.42 (0.06 – 2.01)	0.43 (0.06 – 2.34)	0.46 (0.01 – 31.39)	0.45 (0.07 – 2.25)	0.57 (0.05 – 4.24)	0.79 (0.03 – 33.66)	**INDOIVCONT**	
0.50 (0.22 – 1.07)	0.51 (0.20 – 1.32)	0.58 (0.30 – 1.09)	0.59 (0.29 – 1.18)	0.56 (0.02 – 37.85)	0.62 (0.36 – 1.07)	0.73 (0.15 – 3.81)	1.14 (0.08 – 34.40)	1.37 (0.26 – 9.96)	**PLAC_NORX**

Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for neonatal mortality computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values

eFigure 23. Rankogram for neonatal mortality on sensitivity analysis ('low' & 'probably low' risk of bias studies)



eTable 28. Ranking statistics for neonatal mortality on sensitivity analysis ('low' & 'probably low' risk of bias studies)

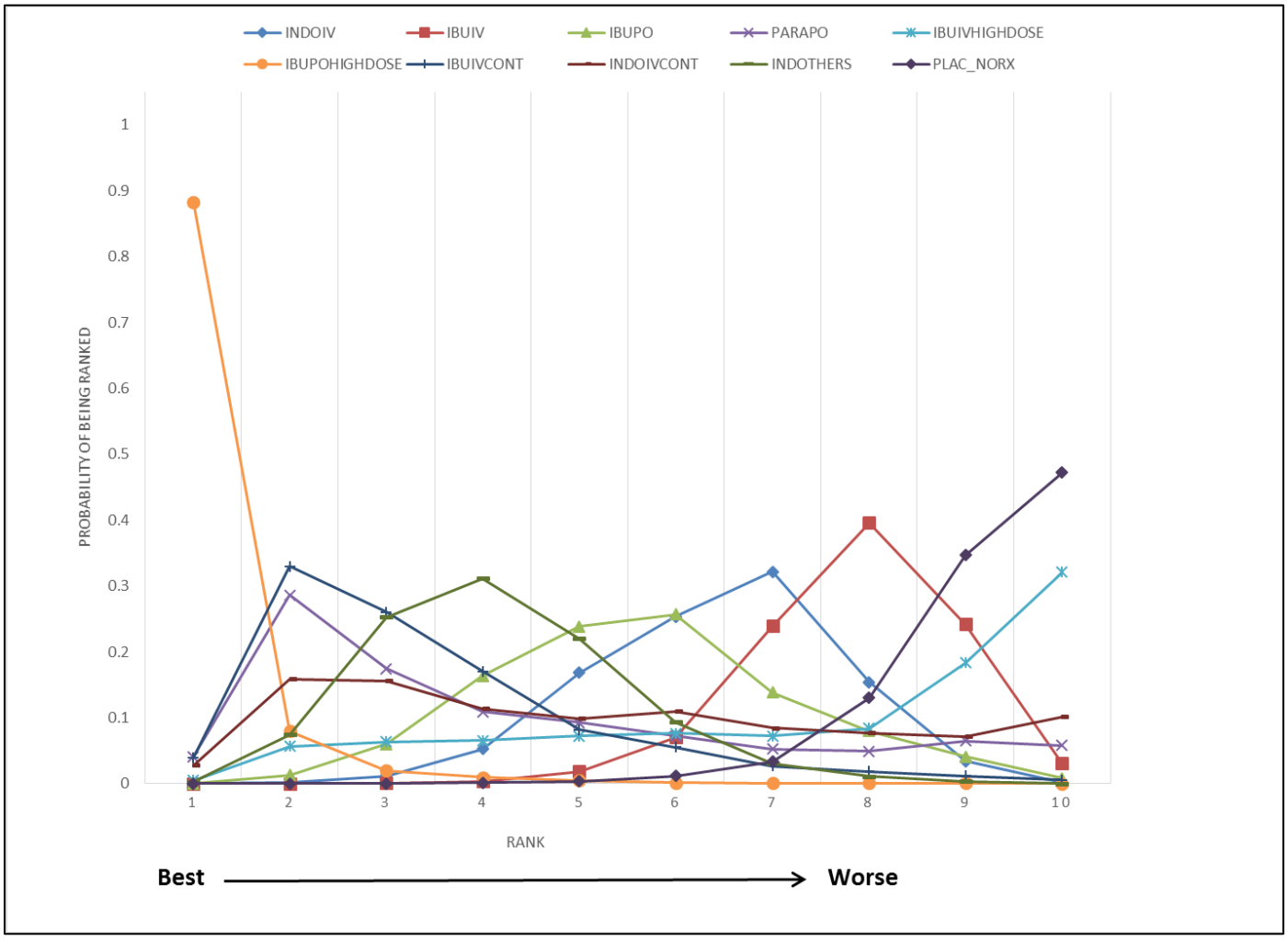
Neonatal Mortality		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95 % Credible intervals)**
INDOIV	0.55 (0.19)	5 (2-8)
IBUIV	0.62 (0.18)	4 (2-8)
IBUPO	0.71 (0.20)	3 (1-7)
PARAPO	0.67 (0.25)	4 (1-9)
IBUIVHIGHDOSE	0.47 (0.33)	6 (1-10)
IBUPOHIGHDOSE	0.37 (0.39)	8 (1-10)
IBUIVCONT	0.55 (0.42)	4 (1-10)
INDOIVCONT	0.25 (0.28)	9 (1-10)
INDOTHERS	0.59 (0.25)	5 (1-9)
PLAC_NORX	0.24 (0.14)	8 (5-10)

eTable 29. Network effect estimates for risk of necrotizing enterocolitis on sensitivity analysis ('low' & 'probably low' risk of bias studies)

IBUPOHIGHDOSE									
0.05 (0.00 – 2.60)	IBUIVCONT								
0.03 (0.00 – 0.87)	0.57 (0.08 – 3.85)	INDOTHERS							
0.03 (0.00 – 2.95)	0.71 (0.03 – 16.93)	1.16 (0.10 – 18.05)	PARAPO						
0.02 (0.00 – 1.83)	0.54 (0.03 – 7.74)	0.89 (0.09 – 11.48)	0.72 (0.02 – 22.85)	INDOIVCONT					
0.02 (0.00 – 0.47)	0.38 (0.04 – 2.59)	0.65 (0.21 – 1.90)	0.56 (0.04 – 5.50)	0.75 (0.05 – 7.10)	IBUPO				
0.01 (0.00 – 0.44)	0.29 (0.05 – 1.80)	0.50 (0.21 – 1.31)	0.42 (0.03 – 5.19)	0.56 (0.05 – 4.98)	0.77 (0.26 – 2.51)	INDOIV			
0.01 (0.00 – 0.61)	0.20 (0.01 – 4.09)	0.35 (0.03 – 4.77)	0.31 (0.01 – 9.35)	0.40 (0.01 – 9.22)	0.54 (0.04 – 7.59)	0.70 (0.06 – 8.19)	IBUIVHIGHDOSE		
0.01 (0.00 – 0.33)	0.22 (0.03 – 1.07)	0.37 (0.14 – 0.92)	0.30 (0.02 – 3.64)	0.42 (0.04 – 3.15)	0.57 (0.19 – 1.66)	0.75 (0.35 – 1.27)	1.08 (0.09 – 10.90)	IBUIV	
0.01 (0.00 – 0.24)	0.13 (0.02 – 0.82)	0.22 (0.10 – 0.48)	0.18 (0.01 – 2.49)	0.24 (0.02 – 2.28)	0.34 (0.10 – 1.10)	0.43 (0.17 – 1.01)	0.62 (0.05 – 7.72)	0.59 (0.24 – 1.52)	PLAC_NORX

Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for risk of necrotizing enterocolitis computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values

eFigure 24. Rankogram for risk of necrotizing enterocolitis on sensitivity analysis ('low' & 'probably low' risk of bias studies)



eTable 30. Ranking statistics for risk of necrotizing enterocolitis on sensitivity analysis ('low' & 'probably low' risk of bias studies)

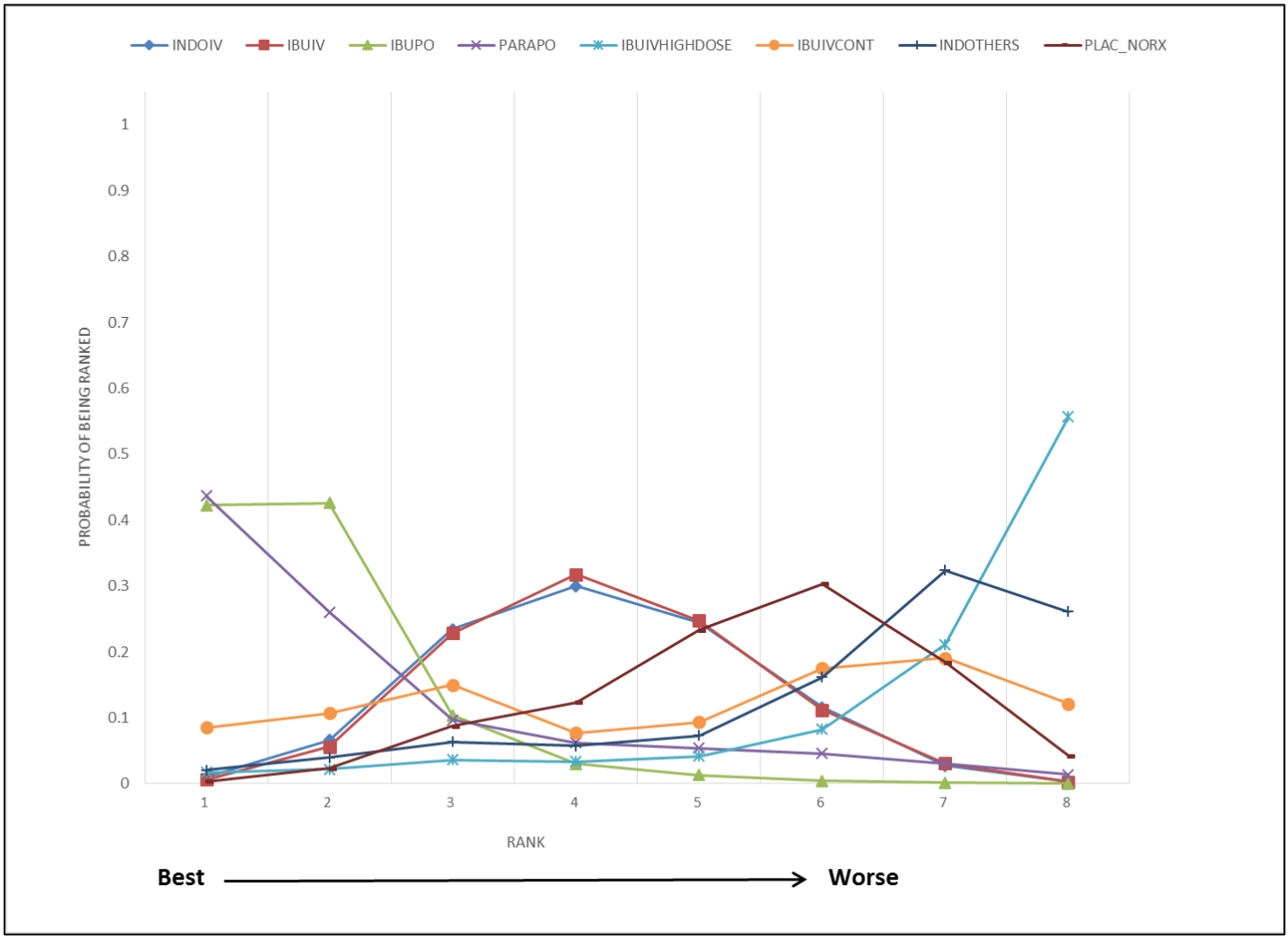
Risk of Necrotizing Enterocolitis		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95% Credible intervals)**
INDOIV	0.39 (0.14)	7 (4-9)
IBUIV	0.24(0.12)	8 (5-10)
IBUPO	0.48 (0.18)	6 (3-9)
PARAPO	0.62 (0.29)	4 (1-10)
IBUIVHIGHDOSE	0.30 (0.30)	8 (2-10)
IBUPOHIGHDOSE	0.97 (0.09)	1 (1-4)
IBUIVCONT	0.74 (0.19)	3 (1-8)
INDOIVCONT	0.55 (0.29)	5 (2-10)
INDOTHERS	0.64 (0.14)	4 (2-7)
PLAC_NORX	0.08 (0.11)	9 (7-10)

eTable 31. Network effect estimates for risk of bronchopulmonary dysplasia on sensitivity analysis ('low' & 'probably low' risk of bias studies)

IBUPO							
0.98 (0.34 – 3.01)	**PARAPO**						
0.60 (0.31 – 1.11)	0.60 (0.20 – 1.75)	**INDOIV**					
0.59 (0.33 – 1.06)	0.60 (0.20 – 1.81)	1.00 (0.67 – 1.51)	**IBUIV**				
0.51 (0.15 – 1.83)	0.52 (0.11 – 2.54)	0.86 (0.28 – 2.93)	0.86 (0.30 – 2.66)	**IBUIVCONT**			
0.49 (0.25 – 0.91)	0.50 (0.16 – 1.53)	0.83 (0.50 – 1.36)	0.83 (0.47 – 1.45)	0.96 (0.26 – 3.17)	**PLAC_NORX**		
0.37 (0.12 – 1.22)	0.39 (0.09 – 1.68)	0.64 (0.23 – 1.74)	0.64 (0.22 – 1.83)	0.72 (0.16 – 3.43)	0.76 (0.26 – 2.33)	**INDOTHERS**	
0.27 (0.07 – 1.09)	0.28 (0.05 – 1.49)	0.46 (0.13 – 1.70)	0.46 (0.14 – 1.58)	0.53 (0.10 – 2.74)	0.55 (0.16 – 2.16)	0.74 (0.15 – 3.51)	**IBUIVHIGHDOSE**

Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for risk of bronchopulmonary dysplasia computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values

eFigure 25. Rankogram for risk of bronchopulmonary dysplasia on sensitivity analysis ('low' & 'probably low' risk of bias studies)



eTable 32. Ranking statistics for risk of bronchopulmonary dysplasia on sensitivity analysis ('low' & 'probably low' risk of bias studies)

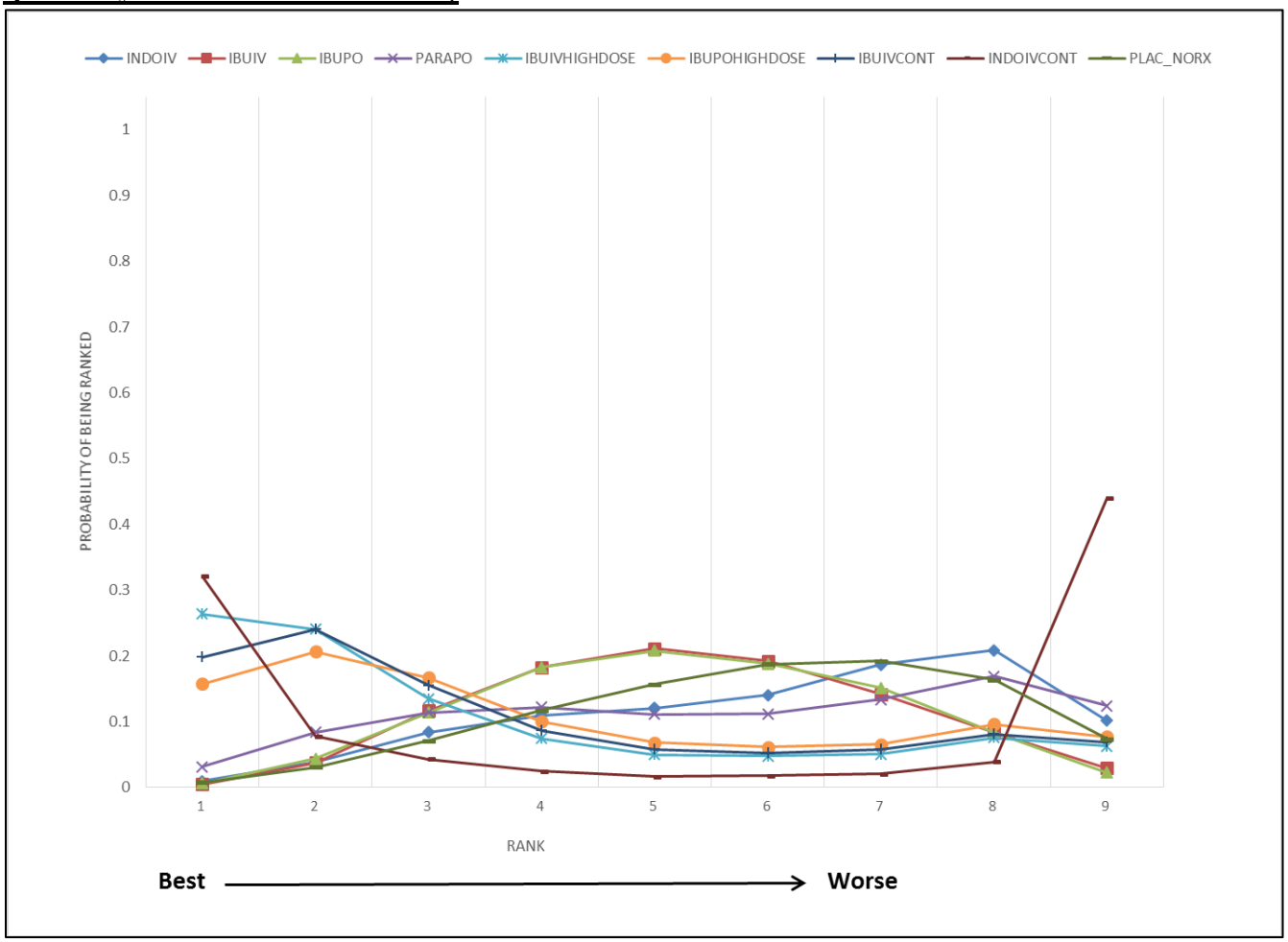
Risk of Bronchopulmonary Dysplasia		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95% Credible intervals)**
INDOIV	0.55 (0.18)	4 (2-7)
IBUIV	0.54 (0.17)	4 (2-7)
IBUPO	0.89 (0.13)	2 (1-4)
PARAPO	0.81 (0.25)	2 (1-7)
IBUIVHIGHDOSE	0.15 (0.24)	8 (2-8)
IBUIVCONT	0.45 (0.32)	5 (1-8)
INDOTHERS	0.26 (0.26)	7 (2-8)
PLAC_NORX	0.37 (0.20)	6 (2-8)

eTable 33. Network effect estimates for risk of intraventricular hemorrhage on sensitivity analysis ('low' & 'probably low' risk of bias studies)

IBUIVHIGHDOSE								
0.90 (0.10 – 7.36)	**IBUIVCONT**							
0.81 (0.09 – 7.05)	0.89 (0.12 – 6.74)	**IBUPOHIGHDOSE**						
0.60 (0.11 – 3.27)	0.67 (0.14 – 3.07)	0.74 (0.20 – 2.69)	**IBUPO**					
0.60 (0.12 – 2.89)	0.68 (0.16 – 2.71)	0.74 (0.18 – 3.06)	1.00 (0.55 – 1.87)	**IBUIV**				
0.50 (0.00 – 209.16)	0.57 (0.00 – 178.25)	0.65 (0.00 – 168.55)	0.85 (0.00 – 239.52)	0.86 (0.00 – 226.35)	**INDOIVCONT**			
0.55 (0.08 – 3.80)	0.63 (0.11 – 3.67)	0.69 (0.14 – 3.41)	0.93 (0.36 – 2.40)	0.93 (0.32 – 2.63)	1.09 (0.00 – 941.60)	**PARAPO**		
0.54 (0.09 – 2.96)	0.60 (0.13 – 2.89)	0.67 (0.16 – 2.73)	0.90 (0.49 – 1.66)	0.90 (0.46 – 1.72)	1.05 (0.00 – 949.67)	0.97 (0.34 – 2.81)	**PLAC_NORX**	
0.52 (0.09 – 3.06)	0.58 (0.11 – 2.94)	0.65 (0.14 – 2.92)	0.87 (0.39 – 1.99)	0.87 (0.39 – 1.96)	1.03 (0.00 – 850.70)	0.93 (0.35 – 2.57)	0.96 (0.43 – 2.21)	**INDOIV**

Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for risk of intraventricular hemorrhage computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values

eFigure 26. Rankogram for risk of intraventricular hemorrhage on sensitivity analysis ('low' & 'probably low' risk of bias studies)



eTable 34. Ranking statistics for risk of intraventricular hemorrhage on sensitivity analysis ('low' & 'probably low' risk of bias studies)

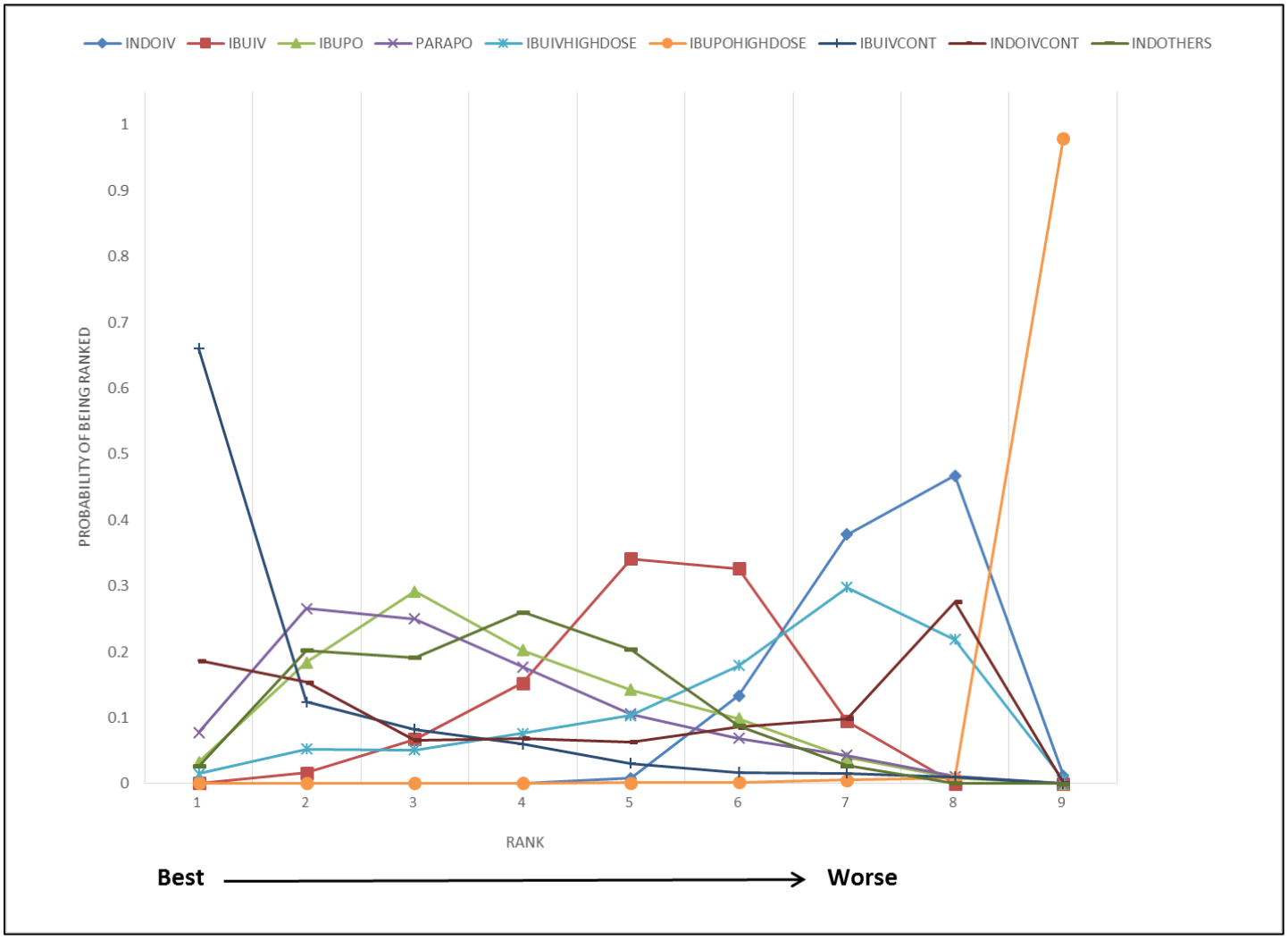
Risk of Intraventricular Hemorrhage		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95% Credible intervals)**
INDOIV	0.36 (0.25)	6 (2-9)
IBUIV	0.46 (0.21)	5 (2-9)
IBUPO	0.47 (0.22)	5 (2-8)
PARAPO	0.42 (0.29)	6 (1-9)
IBUIVHIGHDOSE	0.69 (0.32)	2 (1-9)
IBUPOHIGHDOSE	0.61(0.33)	3 (1-9)
IBUIVCONT	0.65 (0.32)	3 (1-9)
INDOIVCONT	0.46 (0.46)	6 (1-9)
PLAC_NORX	0.38 (0.23)	6 (2-9)

eTable 35. Network effect estimates for risk of oliguria on sensitivity analysis ('low' & 'probably low' risk of bias studies)

IBUIVCONT								
0.13 (0.00 – 9.06)	**PARAPO**							
0.12 (0.00 – 6.47)	0.87 (0.31 – 2.35)	**IBUPO**						
0.11 (0.00 – 3.68)	0.74 (0.07 – 6.78)	0.81 (0.09 – 6.93)	**INDOTHERS**					
0.04 (0.00 – 231.80)	0.51 (0.00 – 342.58)	0.56 (0.00 – 471.92)	0.66 (0.00 – 1621.00)	**INDOIVCONT**				
0.06 (0.00 – 1.88)	0.43 (0.04 – 2.85)	0.48 (0.06 – 2.59)	0.57 (0.21 – 1.57)	0.87 (0.00 – 584.40)	**IBUIV**			
0.03 (0.00 – 2.54)	0.22 (0.01 – 4.44)	0.25 (0.01 – 4.43)	0.32 (0.02 – 3.59)	0.51 (0.00 – 307.80)	0.56 (0.05 – 4.75)	**IBUIVHIGHDOSE**		
0.02 (0.00 – 0.61)	0.14 (0.01 – 0.96)	0.15 (0.02 – 0.93)	0.19 (0.08 – 0.41)	0.28 (0.00 – 197.70)	0.33 (0.19 – 0.55)	0.58 (0.06 – 7.20)	**INDOIV**	
0.00 (0.00 – 0.04)	0.00 (0.00 – 0.09)	0.00 (0.00 – 0.10)	0.00 (0.00 – 0.12)	0.00 (0.00 – 0.12)	0.00 (0.00 – 0.17)	0.00 (0.00 – 0.26)	0.00 (0.00 – 0.57)	**IBUPOHIGHDOSE**

Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for risk of oliguria computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values

eFigure 27. Rankogram for risk of oliguria on sensitivity analysis ('low' & 'probably low' risk of bias studies)



eTable 36. Ranking statistics for risk of oliguria on sensitivity analysis ('low' & 'probably low' risk of bias studies)

Risk of Oliguria		
Treatment	**SUCRA mean (Standard Deviation)**	**Median rank (95% Credible intervals)**
INDOIV	0.21 (0.09)	7 (6-8)
IBUIV	0.48 (0.14)	5 (3-7)
IBUPO	0.66 (0.19)	3 (1-7)
PARAPO	0.70 (0.20)	3 (1-7)
IBUIVHIGHDOSE	0.37(0.23)	7 (2-8)
IBUPOHIGHDOSE	0.006 (0.054)	9 (9-9)
IBUIVCONT	0.89 (0.19)	1 (1-7)
INDOIVCONT	0.54 (0.34)	5 (1-8)
INDOTHERS	0.65 (0.18)	4 (1-7)

eText 3. Guide to interpreting meta-regression results

With a meta-regression model, the pooled relative treatment effect for a certain comparison can be estimated on the basis of available studies, adjusted for differences in the level of the effect modifier between studies. This allows readers to identify the potential effect of some key variables in the results. Usually the approach with meta-regression is, after running the network meta-analysis and obtaining the effect estimates and rankings, a new model is generated adjusting for additional variables that could be effect modifiers (17).

In the following hypothetical example, an NMA of four interventions A, B, C and D, for the treatment of diarrhea in children, was conducted. The outcome of interest was the proportion of children who had diarrhea at day 3 of treatment. Odds ratios (OR) were interpreted as follows: for OR below 1.0, the first displayed intervention was protective (less children with diarrhea at day 3); for OR above 1.0, the opposite. A meta-regression analysis was run adjusting for age and days with diarrhea before recruitment as they were thought to play a role as effect modifiers. The results of this analysis have been displayed in the example tables below (etext3: Example tables A & B). It was found that on adjustment by days with diarrhea before recruitment, estimates for comparisons with treatment D changed substantially, and its SUCRA values changed as well. This suggested that the days with diarrhea had an impact on the effect of treatment D on the presence of diarrhea at day 3. In other words, the more days with diarrhea the child had, the less was the effect of D.

eText3: Example Table A: Hypothetical example of network meta-regression results

Treatment comparison	Meta-regression for Age	Meta-regression for Days of diarrhea before recruitment
A vs B	0.48 (0.18-0.9)	0.48 (0.18-0.82)
B vs C	0.6 (0.4-0.9)	0.6 (0.4-0.9)
A vs C	0.32 (021-0.81)	0.32 (021-0.81)
A vs D	1.05 (0.9-1.4)	**0.58 (0.39-0.89)**
D vs B	0.7 (0.40-0.86)	**1.0 (0.88-1.46)**
D vs C	0.24 (0.2 -0.60)	0.55 (0.35-0.85)

eText3: Example Table B: Hypothetic example of corresponding mean SUCRA values (with SD) in the meta-regression Analysis

Treatment	Meta-regression for Age	Meta-regression for Days of diarrhea before recruitment
A	0.96 (0.12)	0.96 (0.12)
D	**0.95 (0.08)**	**0.28 (0.03)**
B	0.23 (0.04)	0.33 (0.06)
C	0.08 (0.01)	0.09 (0.01)

eTable 37. Meta-regression Analysis Results for Outcome: PDA Closure

Meta-regression NMA Results For Mean Gestational Age		*Meta-regression NMA Results For Mean Birth Weight*		*Meta-regression NMA Results For Year of Publication*		*Meta-regression NMA Results For Age of Initiation of Treatment*	
Treatment Comparison	**Network Meta-regression OR (95% CrI)**	**Treatment Comparison**	**Network Meta-regression OR (95% CrI)**	**Treatment Comparison**	**Network Meta-regression OR (95% CrI)**	**Treatment Comparison**	**Network Meta-regression OR (95% CrI)**
PARAPO *versus*		PARAPO *versus*		PARAPO *versus*		PARAPO *versus*	
INDOTHERS	1.99 (0.80-4.86)	INDOTHERS	2.24 (0.93-5.50)	INDOTHERS	1.42 (0.62-3.27)	INDOTHERS	0.95 (0.34-2.73)
INDOIVCONT	2.31 (0.60-9.17)	INDOIVCONT	2.48 (0.66-9.51)	INDOIVCONT	1.43 (0.38-5.47)	INDOIVCONT	0.65 (0.11-3.55)
INDOIV	1.79 (0.77-4.15)	INDOIV	1.97 (0.85-4.55)	INDOIV	1.25 (0.54-2.86)	INDOIV	0.93 (0.30-2.82)
IBUPOHIGHDOSE	0.47 (0.12-1.78)	IBUPOHIGHDOSE	0.53 (0.15-1.93)	IBUPOHIGHDOSE	0.24 (0.06-0.88)	IBUPO	1.11 (0.50-2.47)
IBUPO	1.32 (0.66-2.65)	IBUPO	1.47 (0.75-2.94)	IBUPO	0.93 (0.48-1.81)	IBUIVCONT	2.21 (0.48-9.97)
IBUIVHIGHDOSE	0.91 (0.13-5.84)	IBUIVHIGHDOSE	1.13 (0.18-7.19)	IBUIVHIGHDOSE	0.64 (0.12-3.32)	IBUIV	1.38 (0.43-4.30)
IBUIVCONT	4.40 (0.91-21.77)	IBUIVCONT	5.26 (1.16-24.64)	IBUIVCONT	3.53 (0.91-13.95)	PLAC/NORX	5.89 (2.03-17.91)
IBUIV	3.01 (1.26-7.32)	IBUIV	3.38 (1.44-8.25)	IBUIV	1.94 (0.85-4.56)	INDOTHERS *versus*	
PLAC/NORX	15.92 (6.50-41.74)	PLAC/NORX	18.58 (7.40-48.49)	PLAC/NORX	8.86 (3.60-22.98)	INDOIVCONT	0.68 (0.15-2.75)
INDOTHERS *versus*		INDOTHERS *versus*		INDOTHERS *versus*		INDOIV	0.96 (0.58-1.59)
INDOIVCONT	1.16 (0.36-3.88)	INDOIVCONT	1.10 (0.36-3.53)	INDOIVCONT	1.01 (0.33-3.14)	IBUPO	1.16 (0.60-2.30)
INDOIV	0.90 (0.59-1.37)	INDOIV	0.87 (0.58-1.31)	INDOIV	0.88 (0.59-1.29)	IBUIVCONT	2.32 (0.69-7.66)
IBUPOHIGHDOSE	0.24 (0.07-0.80)	IBUPOHIGHDOSE	0.24 (0.07-0.78)	IBUPOHIGHDOSE	0.17 (0.05-0.54)	IBUIV	1.46 (0.77-2.69)
IBUPO	0.67 (0.38-1.18)	IBUPO	0.66 (0.37-1.14)	IBUPO	0.65 (0.38-1.12)	PLAC/NORX	6.10 (3.39-11.95)
IBUIVHIGHDOSE	0.46 (0.08-2.41)	IBUIVHIGHDOSE	0.51 (0.10-2.56)	IBUIVHIGHDOSE	0.45 (0.09-2.11)	INDOIVCONT *versus*	
IBUIVCONT	2.24 (0.57-8.87)	IBUIVCONT	2.34 (0.64-8.69)	IBUIVCONT	2.47 (0.72-8.95)	INDOIV	1.42 (0.38-5.76)
IBUIV	1.52 (0.90-2.62)	IBUIV	1.51 (0.91-2.57)	IBUIV	1.37 (0.83-2.32)	IBUPO	1.71 (0.38-8.35)
PLAC/NORX	8.05 (4.48-15.14)	PLAC/NORX	8.24 (4.70-15.27)	PLAC/NORX	6.25 (3.61-11.34)	IBUIVCONT	3.39 (0.67-18.43)
INDOIVCONT *versus*		INDOIVCONT *versus*		INDOIVCONT *versus*		IBUIV	2.13 (0.62-8.09)
INDOIV	0.78 (0.25-2.30)	INDOIV	0.79 (0.27-2.28)	INDOIV	0.87 (0.30-2.46)	PLAC/NORX	9.05 (2.18-42.52)
IBUPOHIGHDOSE	0.20 (0.04-1.04)	IBUPOHIGHDOSE	0.22 (0.04-1.02)	IBUPOHIGHDOSE	0.17 (0.04-0.74)	INDOIV *versus*	
IBUPO	0.58 (0.17-1.89)	IBUPO	0.59 (0.18-1.89)	IBUPO	0.65 (0.21-1.99)	IBUPO	1.20 (0.57-2.59)
IBUIVHIGHDOSE	0.39 (0.05-2.86)	IBUIVHIGHDOSE	0.46 (0.06-2.97)	IBUIVHIGHDOSE	0.44 (0.07-2.72)	IBUIVCONT	2.39 (0.78-7.49)
IBUIVCONT	1.92 (0.34-10.43)	IBUIVCONT	2.12 (0.40-10.52)	IBUIVCONT	2.44 (0.49-12.00)	IBUIV	1.50 (0.97-2.38)
IBUIV	1.31 (0.43-3.95)	IBUIV	1.37 (0.47-3.91)	IBUIV	1.35 (0.48-3.83)	PLAC/NORX	6.34 (3.32-12.90)
PLAC/NORX	6.95 (1.95-24.51)	PLAC/NORX	7.46 (2.29-24.73)	PLAC/NORX	6.17 (2.02-19.16)	IBUPO *versus*	
INDOIV *versus*		INDOIV *versus*		INDOIV *versus*		IBUIVCONT	2.00 (0.54-7.17)
IBUPOHIGHDOSE	0.26 (0.08-0.90)	IBUPOHIGHDOSE	0.27 (0.08-0.87)	IBUPOHIGHDOSE	0.19 (0.06-0.59)	IBUIV	1.25 (0.55-2.79)
IBUPO	0.74 (0.43-1.28)	IBUPO	0.75 (0.44-1.28)	IBUPO	0.74 (0.46-1.22)	PLAC/NORX	5.24 (2.60-11.22)
IBUIVHIGHDOSE	0.51 (0.09-2.65)	IBUIVHIGHDOSE	0.58 (0.11-2.88)	IBUIVHIGHDOSE	0.51 (0.11-2.30)	IBUIVCONT *versus*	
IBUIVCONT	2.47 (0.64-9.66)	IBUIVCONT	2.67 (0.76-9.53)	IBUIVCONT	2.80 (0.84-9.98)	IBUIV	0.62 (0.23-1.74)
IBUIV	1.69 (1.12-2.59)	IBUIV	1.72 (1.17-2.61)	IBUIV	1.56 (1.08-2.30)	PLAC/NORX	2.66 (0.77-9.62)
PLAC/NORX	8.91 (4.82-17.22)	PLAC/NORX	9.41 (5.36-17.51)	PLAC/NORX	7.08 (4.35-12.34)	IBUIV *versus*	
IBUPOHIGHDOSE *versus*		IBUPOHIGHDOSE *versus*		IBUPOHIGHDOSE *versus*		PLAC/NORX	4.24 (2.16-8.83)
IBUPO	2.84 (0.95-8.52)	IBUPO	2.75 (0.97-7.93)	IBUPO	3.91 (1.40-10.87)		
IBUIVHIGHDOSE	1.93 (0.26-14.06)	IBUIVHIGHDOSE	2.13 (0.30-14.60)	IBUIVHIGHDOSE	2.70 (0.40-17.60)		
IBUIVCONT	9.52 (1.66-55.73)	IBUIVCONT	9.76 (1.85-52.78)	IBUIVCONT	14.73 (2.90-77.76)		
IBUIV	6.46 (1.90-22.01)	IBUIV	6.31 (1.98-20.49)	IBUIV	8.21 (2.69-25.46)		
PLAC/NORX	34.15 (10.00-121.90)	PLAC/NORX	34.60 (10.74-117.80)	PLAC/NORX	37.47 (12.32-119.00)		
IBUPO *versus*		IBUPO *versus*		IBUPO *versus*			
IBUIVHIGHDOSE	0.68 (0.12-3.71)	IBUIVHIGHDOSE	0.77 (0.14-3.96)	IBUIVHIGHDOSE	0.69 (0.14-3.17)		
IBUIVCONT	3.37 (0.83-13.66)	IBUIVCONT	3.56 (0.95-13.75)	IBUIVCONT	3.79 (1.09-13.44)		
IBUIV	2.28 (1.31-4.01)	IBUIV	2.30 (1.35-4.03)	IBUIV	2.10 (1.29-3.46)		
PLAC/NORX	12.03 (6.64-23.25)	PLAC/NORX	12.56 (7.00-23.66)	PLAC/NORX	9.56 (5.52-17.29)		
IBUIVHIGHDOSE *versus*		IBUIVHIGHDOSE *versus*		IBUIVHIGHDOSE *versus*			
IBUIVCONT	4.87 (0.68-37.63)	IBUIVCONT	4.66 (0.67-33.94)	IBUIVCONT	5.55 (0.87-37.28)		
IBUIV	3.32 (0.68-17.00)	IBUIV	2.98 (0.65-14.78)	IBUIV	3.04 (0.71-13.99)		
PLAC/NORX	17.68 (3.29-103.90)	PLAC/NORX	16.15 (3.19-91.47)	PLAC/NORX	13.86 (2.93-71.25)		
IBUIVCONT *versus*		IBUIVCONT *versus*		IBUIVCONT *versus*			
IBUIV	0.68 (0.19-2.42)	IBUIV	0.64 (0.20-2.12)	IBUIV	0.55 (0.17-1.77)		
PLAC/NORX	3.60 (0.88-15.19)	PLAC/NORX	3.53 (0.93-13.95)	PLAC/NORX	2.52 (0.68-9.46)		
IBUIV *versus*		IBUIV *versus*		IBUIV *versus*			
PLAC/NORX	5.30 (2.81-10.22)	PLAC/NORX	5.47 (3.02-10.38)	PLAC/NORX	4.55 (2.69-8.01)		
Common within-network between-study variance	0.23 (0.04-0.57)	Common within-network between-study variance	0.20 (0.02-0.50)	Common within-network between-study variance	0.17 (0.01-0.45)	Common within-network between-study variance	0.06 (0.00-0.48)
Regression coefficient (log OR scale)	-0.039 (-0.172-0.096)	Regression coefficient (log OR scale)	-0.001 (-0.001-0.000)	Regression coefficient (log OR scale)	0.022 (-0.002-0.047)	Regression coefficient (log OR scale)	-0.045 (-0.102-0.014)

eTable 38. Meta-regression Analysis Corresponding SUCRA values: PDA Closure

Mean Gestational Age		Mean Birth Weight		Year of Publication		Age initiation of Treatment	
Treatment	**Mean SUCRA (SD)**	**Treatment**	**Mean SUCRA (SD)**	**Treatment**	**Mean SUCRA (SD)**	**Treatment**	**Mean SUCRA (SD)**
PARAPO	0.79 (0.15)	PARAPO	0.82 (0.13)	PARAPO	0.65 (0.19)	PARAPO	0.63 (0.28)
INDOTHERS	0.45 (0.13)	INDOTHERS	0.44 (0.13)	INDOTHERS	0.44 (0.14)	INDOTHERS	0.68 (0.19)
INDOIVCONT	0.41 (0.23)	INDOIVCONT	0.42 (0.22)	INDOIVCONT	0.47 (0.24)	INDOIVCONT	0.81 (0.27)
INDOIV	0.52 (0.12)	INDOIV	0.53 (0.11)	INDOIV	0.54 (0.12)	INDOIV	0.72 (0.18)
IBUPOHIGHDOSE	0.95 (0.10)	IBUPOHIGHDOSE	0.95 (0.10)	IBUPOHIGHDOSE	0.98 (0.05)	IBUPO	0.55 (0.22)
IBUPO	0.68 (0.11)	IBUPO	0.68 (0.11)	IBUPO	0.72 (0.11)	IBUIVCONT	0.23 (0.20)
IBUIVHIGHDOSE	0.76 (0.24)	IBUIVHIGHDOSE	0.72 (0.25)	IBUIVHIGHDOSE	0.77 (0.23)	IBUIV	0.38 (0.16)
IBUIVCONT	0.20 (0.17)	IBUIVCONT	0.18 (0.15)	IBUIVCONT	0.16 (0.14)	PLAC/NORX	0.01 (0.03)
IBUIV	0.24 (0.08)	IBUIV	0.24 (0.08)	IBUIV	0.26 (0.09)		
PLAC/NORX	0.00 (0.02)	PLAC/NORX	0.00 (0.02)	PLAC/NORX	0.01 (0.03)		

eTable 39. Meta-regression Analysis Results for Outcome: Need for repeat pharmacotherapy

Meta-regression NMA Results For Mean Gestational Age		*Meta-regression NMA Results For Mean Birth Weight*		*Meta-regression NMA Results For Year of Publication*		*Meta-regression NMA Results For Age of Initiation of Treatment*	
Treatment Comparison	**Network Meta-regression OR (95% CrI)**	**Treatment Comparison**	**Network Meta-regression OR (95% CrI)**	**Treatment Comparison**	**Network Meta-regression OR (95% CrI)**	**Treatment Comparison**	**Network Meta-regression OR (95% CrI)**
PARAPO *versus*		PARAPO *versus*		PARAPO *versus*		PARAPO *versus*	
INDOTHERS	0.77 (0.29-2.21)	INDOTHERS	0.79 (0.28-2.24)	INDOTHERS	0.78 (0.27-2.29)	INDOTHERS	0.67 (0.11-3.45)
INDOIVCONT	0.44 (0.10-2.06)	INDOIVCONT	0.46 (0.10-2.17)	INDOIVCONT	0.58 (0.09-3.99)	INDOIVCONT	0.35 (0.02-3.78)
INDOIV	0.47 (0.19-1.25)	INDOIV	0.48 (0.19-1.26)	INDOIV	0.54 (0.17-1.85)	INDOIV	0.34 (0.04-1.93)
IBUPOHIGHDOSE	1.97 (0.42-9.94)	IBUPOHIGHDOSE	1.86 (0.41-8.92)	IBUPOHIGHDOSE	1.93 (0.38-11.04)	IBUPO	0.51 (0.12-1.94)
IBUPO	0.85 (0.45-1.67)	IBUPO	0.87 (0.44-1.72)	IBUPO	0.87 (0.42-1.88)	IBUIV	0.25 (0.03-1.56)
IBUIVHIGHDOSE	1.37 (0.25-8.51)	IBUIVHIGHDOSE	1.39 (0.24-8.72)	IBUIVHIGHDOSE	1.27 (0.25-7.02)	PLAC/NORX	0.06 (0.01-0.39)
IBUIV	0.32 (0.13-0.79)	IBUIV	0.32 (0.12-0.83)	IBUIV	0.37 (0.11-1.32)	INDOTHERS *versus*	
PLAC/NORX	0.08 (0.02-0.28)	PLAC/NORX	0.07 (0.02-0.23)	PLAC/NORX	0.08 (0.02-0.37)	INDOIVCONT	0.52 (0.06-3.16)
INDOTHERS *versus*		INDOTHERS *versus*		INDOTHERS *versus*		INDOIV	0.50 (0.15-1.29)
INDOIVCONT	0.58 (0.14-2.37)	INDOIVCONT	0.59 (0.14-2.35)	INDOIVCONT	0.75 (0.17-3.50)	IBUPO	0.75 (0.25-2.48)
INDOIV	0.61 (0.35-1.05)	INDOIV	0.61 (0.36-1.07)	INDOIV	0.69 (0.40-1.23)	IBUIV	0.37 (0.10-1.09)
IBUPOHIGHDOSE	2.56 (0.59-11.58)	IBUPOHIGHDOSE	2.35 (0.56-10.71)	IBUPOHIGHDOSE	2.47 (0.59-11.33)	PLAC/NORX	0.09 (0.02-0.28)
IBUPO	1.10 (0.56-2.21)	IBUPO	1.10 (0.56-2.20)	IBUPO	1.12 (0.59-2.15)	INDOIVCONT *versus*	
IBUIVHIGHDOSE	1.77 (0.42-8.09)	IBUIVHIGHDOSE	1.76 (0.42-8.35)	IBUIVHIGHDOSE	1.63 (0.39-7.12)	INDOIV	0.96 (0.18-5.03)
IBUIV	0.41 (0.21-0.77)	IBUIV	0.41 (0.21-0.78)	IBUIV	0.48 (0.24-0.96)	IBUPO	1.45 (0.21-13.99)
PLAC/NORX	0.10 (0.04-0.23)	PLAC/NORX	0.09 (0.04-0.20)	PLAC/NORX	0.10 (0.04-0.26)	IBUIV	0.72 (0.15-3.13)
INDOIVCONT *versus*		INDOIVCONT *versus*		INDOIVCONT *versus*		PLAC/NORX	0.17 (0.03-0.99)
INDOIV	1.06 (0.28-3.85)	INDOIV	1.04 (0.29-3.93)	INDOIV	0.93 (0.23-3.50)	INDOIV *versus*	
IBUPOHIGHDOSE	4.44 (0.62-31.52)	IBUPOHIGHDOSE	4.08 (0.57-29.66)	IBUPOHIGHDOSE	3.27 (0.48-21.76)	IBUPO	1.51 (0.45-7.35)
IBUPO	1.92 (0.47-7.35)	IBUPO	1.90 (0.46-7.46)	IBUPO	1.48 (0.31-6.64)	IBUIV	0.76 (0.33-1.60)
IBUIVHIGHDOSE	3.08 (0.49-21.79)	IBUIVHIGHDOSE	2.97 (0.45-20.26)	IBUIVHIGHDOSE	2.19 (0.32-14.91)	PLAC/NORX	0.18 (0.06-0.49)
IBUIV	0.71 (0.20-2.33)	IBUIV	0.70 (0.20-2.35)	IBUIV	0.64 (0.18-2.16)	IBUPO *versus*	
PLAC/NORX	0.17 (0.04-0.77)	PLAC/NORX	0.15 (0.03-0.64)	PLAC/NORX	0.13 (0.03-0.55)	IBUIV	0.50 (0.09-1.87)
INDOIV *versus*		INDOIV *versus*		INDOIV *versus*		PLAC/NORX	0.12 (0.02-0.46)
IBUPOHIGHDOSE	4.16 (0.96-19.01)	IBUPOHIGHDOSE	3.86 (0.91-16.92)	IBUPOHIGHDOSE	3.56 (0.87-15.28)	IBUIV *versus*	
IBUPO	1.80 (0.94-3.44)	IBUPO	1.80 (0.95-3.41)	IBUPO	1.61 (0.78-3.18)	PLAC/NORX	0.24 (0.08-0.68)
IBUIVHIGHDOSE	2.92 (0.69-13.38)	IBUIVHIGHDOSE	2.86 (0.67-12.89)	IBUIVHIGHDOSE	2.35 (0.58-9.96)		
IBUIV	0.68 (0.42-1.03)	IBUIV	0.67 (0.41-1.03)	IBUIV	0.69 (0.43-1.08)		
PLAC/NORX	0.17 (0.07-0.37)	PLAC/NORX	0.15 (0.07-0.30)	PLAC/NORX	0.15 (0.07-0.32)		
IBUPOHIGHDOSE *versus*		IBUPOHIGHDOSE *versus*		IBUPOHIGHDOSE *versus*			
IBUPO	0.44 (0.11-1.68)	IBUPO	0.47 (0.12-1.74)	IBUPO	0.45 (0.11-1.71)		
IBUIVHIGHDOSE	0.69 (0.09-5.64)	IBUIVHIGHDOSE	0.74 (0.10-5.70)	IBUIVHIGHDOSE	0.65 (0.09-4.73)		
IBUIV	0.16 (0.03-0.70)	IBUIV	0.17 (0.04-0.75)	IBUIV	0.19 (0.05-0.78)		
PLAC/NORX	0.04 (0.01-0.20)	PLAC/NORX	0.04 (0.01-0.18)	PLAC/NORX	0.04 (0.01-0.20)		
IBUPO *versus*		IBUPO *versus*		IBUPO *versus*			
IBUIVHIGHDOSE	1.63 (0.36-7.98)	IBUIVHIGHDOSE	1.59 (0.35-7.87)	IBUIVHIGHDOSE	1.46 (0.35-6.29)		
IBUIV	0.37 (0.19-0.69)	IBUIV	0.37 (0.19-0.69)	IBUIV	0.43 (0.21-0.90)		
PLAC/NORX	0.09 (0.04-0.24)	PLAC/NORX	0.08 (0.03-0.20)	PLAC/NORX	0.09 (0.03-0.27)		
IBUIVHIGHDOSE *versus*		IBUIVHIGHDOSE *versus*		IBUIVHIGHDOSE *versus*			
IBUIV	0.23 (0.05-0.90)	IBUIV	0.24 (0.05-0.90)	IBUIV	0.30 (0.07-1.15)		
PLAC/NORX	0.06 (0.01-0.26)	PLAC/NORX	0.05 (0.01-0.23)	PLAC/NORX	0.06 (0.01-0.31)		
IBUIV *versus*		IBUIV *versus*		IBUIV *versus*			
PLAC/NORX	0.25 (0.11-0.56)	PLAC/NORX	0.22 (0.10-0.46)	PLAC/NORX	0.21 (0.10-0.45)		
Common within-network between-study variance	0.05 (0.00-0.40)	Common within-network between-study variance	0.04 (0.00-0.39)	Common within-network between-study variance	0.04 (0.00-0.36)	Common within-network between-study variance	0.10 (0.00-1.42)
Regression coefficient (log OR scale)	-0.052 (-0.223-0.106)	Regression coefficient (log OR scale)	0.000 (-0.002-0.001)	Regression coefficient (log OR scale)	-0.009 (-0.053-0.032)	Regression coefficient (log OR scale)	-0.047 (-0.197-0.088)

eTable 40. Meta-regression Analysis Corresponding SUCRA values: Need for repeat pharmacotherapy

Mean Gestational Age		**Mean Birth Weight**		**Year of Publication**		**Age of initiation of Treatment**	
Treatment	**Mean SUCRA (SD)**	**Treatment**	**Mean SUCRA (SD)**	**Treatment**	**Mean SUCRA (SD)**	**Treatment**	**Mean SUCRA (SD)**
PARAPO	0.71 (0.19)	PARAPO	0.71 (0.19)	PARAPO	0.68 (0.24)	PARAPO	0.87 (0.21)
INDOTHERS	0.59 (0.16)	INDOTHERS	0.60 (0.16)	INDOTHERS	0.57 (0.17)	INDOTHERS	0.78 (0.17)
INDOIVCONT	0.36 (0.23)	INDOIVCONT	0.37 (0.24)	INDOIVCONT	0.44 (0.28)	INDOIVCONT	0.49 (0.29)
INDOIV	0.34 (0.10)	INDOIV	0.34 (0.10)	INDOIV	0.36 (0.13)	INDOIV	0.45 (0.18)
IBUPOHIGHDOSE	0.89 (0.17)	IBUPOHIGHDOSE	0.88 (0.18)	IBUPOHIGHDOSE	0.88 (0.18)	IBUPO	0.62 (0.21)
IBUPO	0.64 (0.13)	IBUPO	0.64 (0.13)	IBUPO	0.63 (0.14)	IBUIV	0.29 (0.16)
IBUIVHIGHDOSE	0.79 (0.22)	IBUIVHIGHDOSE	0.79 (0.23)	IBUIVHIGHDOSE	0.75 (0.25)	PLAC/NORX	0.01 (0.04)
IBUIV	0.17 (0.07)	IBUIV	0.17 (0.07)	IBUIV	0.18 (0.08)		
PLAC/NORX	0.00 (0.02)	PLAC/NORX	0.00 (0.01)	PLAC/NORX	0.00 (0.01)		

eTable 41. Meta-regression Analysis Results for Outcome: Neonatal Mortality

Meta-regression NMA Results For Mean Gestational Age		*Meta-regression NMA Results For Mean Birth Weight*		*Meta-regression NMA Results For Year of Publication*		*Meta-regression NMA Results For Age of Initiation of Treatment*	
Treatment Comparison	**Network Meta-regression OR (95% CrI)**	**Treatment Comparison**	**Network Meta-regression OR (95% CrI)**	**Treatment Comparison**	**Network Meta-regression OR (95% CrI)**	**Treatment Comparison**	**Network Meta-regression OR (95% CrI)**
PARAPO *versus*		PARAPO *versus*		PARAPO *versus*		INDOTHERS *versus*	
INDOTHERS	0.75 (0.29-1.91)	INDOTHERS	0.80 (0.32-2.01)	INDOTHERS	0.78 (0.31-1.98)	INDOIVCONT	0.77 (0.09-6.22)
INDOIVCONT	0.40 (0.06-2.44)	INDOIVCONT	0.42 (0.06-2.32)	INDOIVCONT	0.44 (0.06-2.86)	INDOIV	0.94 (0.46-1.85)
INDOIV	0.86 (0.37-2.01)	INDOIV	0.88 (0.39-2.04)	INDOIV	0.91 (0.36-2.30)	IBUPO	2.33 (0.80-7.46)
IBUPOHIGHDOSE	0.37 (0.01-6.53)	IBUPOHIGHDOSE	0.45 (0.01-7.33)	IBUPOHIGHDOSE	0.43 (0.01-8.05)	IBUIVCONT	1.17 (0.02-55.69)
IBUPO	1.00 (0.46-2.24)	IBUPO	1.05 (0.49-2.27)	IBUPO	1.07 (0.47-2.55)	IBUIV	1.12 (0.47-2.73)
IBUIVHIGHDOSE	0.72 (0.12-4.73)	IBUIVHIGHDOSE	0.86 (0.15-5.03)	IBUIVHIGHDOSE	0.79 (0.15-4.47)	PLAC/NORX	0.65 (0.32-1.26)
IBUIVCONT	0.91 (0.02-37.98)	IBUIVCONT	1.03 (0.02-58.09)	IBUIVCONT	0.89 (0.02-29.27)	INDOIVCONT *versus*	
IBUIV	0.94 (0.38-2.40)	IBUIV	0.97 (0.41-2.40)	IBUIV	1.03 (0.37-2.97)	INDOIV	1.19 (0.16-9.46)
PLAC/NORX	0.56 (0.22-1.39)	PLAC/NORX	0.61 (0.25-1.49)	PLAC/NORX	0.61 (0.23-1.70)	IBUPO	3.04 (0.31-30.75)
INDOTHERS *versus*		INDOTHERS *versus*		INDOTHERS *versus*		IBUIVCONT	1.55 (0.02-95.81)
INDOIVCONT	0.54 (0.08-2.84)	INDOIVCONT	0.53 (0.08-2.59)	INDOIVCONT	0.57 (0.09-2.97)	IBUIV	1.45 (0.23-9.84)
INDOIV	1.15 (0.74-1.82)	INDOIV	1.11 (0.71-1.73)	INDOIV	1.18 (0.73-1.88)	PLAC/NORX	0.82 (0.11-6.57)
IBUPOHIGHDOSE	0.50 (0.01-7.63)	IBUPOHIGHDOSE	0.56 (0.02-8.37)	IBUPOHIGHDOSE	0.57 (0.01-9.35)	INDOIV *versus*	
IBUPO	1.35 (0.71-2.56)	IBUPO	1.31 (0.67-2.55)	IBUPO	1.38 (0.70-2.71)	IBUPO	2.48 (0.84-8.16)
IBUIVHIGHDOSE	0.97 (0.19-4.90)	IBUIVHIGHDOSE	1.07 (0.23-5.25)	IBUIVHIGHDOSE	1.02 (0.21-4.92)	IBUIVCONT	1.26 (0.02-58.52)
IBUIVCONT	1.19 (0.03-46.44)	IBUIVCONT	1.28 (0.03-70.42)	IBUIVCONT	1.14 (0.02-37.29)	IBUIV	1.20 (0.62-2.45)
IBUIV	1.28 (0.69-2.41)	IBUIV	1.21 (0.66-2.32)	IBUIV	1.33 (0.67-2.60)	PLAC/NORX	0.69 (0.39-1.24)
PLAC/NORX	0.74 (0.44-1.28)	PLAC/NORX	0.75 (0.45-1.32)	PLAC/NORX	0.79 (0.43-1.47)	IBUPO *versus*	
INDOIVCONT *versus*		INDOIVCONT *versus*		INDOIVCONT *versus*		IBUIVCONT	0.50 (0.01-25.72)
INDOIV	2.14 (0.42-13.28)	INDOIV	2.10 (0.47-12.92)	INDOIV	2.07 (0.43-11.65)	IBUIV	0.48 (0.13-1.63)
IBUPOHIGHDOSE	0.95 (0.02-25.30)	IBUPOHIGHDOSE	1.05 (0.03-29.01)	IBUPOHIGHDOSE	0.95 (0.02-25.98)	PLAC/NORX	0.28 (0.09-0.79)
IBUPO	2.51 (0.45-16.41)	IBUPO	2.51 (0.51-15.12)	IBUPO	2.42 (0.48-14.84)	IBUIVCONT *versus*	
IBUIVHIGHDOSE	1.78 (0.19-18.14)	IBUIVHIGHDOSE	2.11 (0.25-21.54)	IBUIVHIGHDOSE	1.81 (0.21-17.39)	IBUIV	0.97 (0.02-56.04)
IBUIVCONT	2.23 (0.04-136.70)	IBUIVCONT	2.56 (0.05-179.90)	IBUIVCONT	1.98 (0.03-86.87)	PLAC/NORX	0.54 (0.01-36.77)
IBUIV	2.37 (0.48-13.56)	IBUIV	2.29 (0.54-13.45)	IBUIV	2.30 (0.51-12.69)	IBUIV *versus*	
PLAC/NORX	1.39 (0.25-8.66)	PLAC/NORX	1.43 (0.31-8.98)	PLAC/NORX	1.38 (0.29-7.86)	PLAC/NORX	0.58 (0.28-1.16)
INDOIV *versus*		INDOIV *versus*		INDOIV *versus*			
IBUPOHIGHDOSE	0.43 (0.01-6.88)	IBUPOHIGHDOSE	0.51 (0.02-7.81)	IBUPOHIGHDOSE	0.47 (0.01-8.00)		
IBUPO	1.17 (0.65-2.11)	IBUPO	1.18 (0.65-2.17)	IBUPO	1.17 (0.65-2.17)		
IBUIVHIGHDOSE	0.84 (0.17-4.36)	IBUIVHIGHDOSE	0.97 (0.21-4.67)	IBUIVHIGHDOSE	0.87 (0.19-4.05)		
IBUIVCONT	1.04 (0.03-39.00)	IBUIVCONT	1.16 (0.03-62.43)	IBUIVCONT	0.97 (0.02-30.28)		
IBUIV	1.10 (0.68-1.81)	IBUIV	1.10 (0.67-1.80)	IBUIV	1.13 (0.69-1.87)		
PLAC/NORX	0.65 (0.40-1.04)	PLAC/NORX	0.68 (0.42-1.09)	PLAC/NORX	0.67 (0.42-1.07)		
IBUPOHIGHDOSE *versus*		IBUPOHIGHDOSE *versus*		IBUPOHIGHDOSE *versus*			
IBUPO	2.72 (0.18-90.56)	IBUPO	2.31 (0.16-65.91)	IBUPO	2.48 (0.16-103.90)		
IBUIVHIGHDOSE	2.00 (0.08-90.59)	IBUIVHIGHDOSE	1.94 (0.09-74.02)	IBUIVHIGHDOSE	1.84 (0.07-86.77)		
IBUIVCONT	2.50 (0.02-350.10)	IBUIVCONT	2.59 (0.03-426.10)	IBUIVCONT	2.22 (0.02-254.30)		
IBUIV	2.55 (0.15-90.95)	IBUIV	2.15 (0.14-65.74)	IBUIV	2.40 (0.15-105.50)		
PLAC/NORX	1.52 (0.09-49.98)	PLAC/NORX	1.33 (0.09-40.32)	PLAC/NORX	1.43 (0.08-64.01)		
IBUPO *versus*		IBUPO *versus*		IBUPO *versus*			
IBUIVHIGHDOSE	0.72 (0.13-3.79)	IBUIVHIGHDOSE	0.82 (0.16-4.15)	IBUIVHIGHDOSE	0.73 (0.15-3.60)		
IBUIVCONT	0.89 (0.03-33.53)	IBUIVCONT	0.97 (0.02-51.56)	IBUIVCONT	0.82 (0.02-25.78)		
IBUIV	0.95 (0.50-1.82)	IBUIV	0.92 (0.48-1.78)	IBUIV	0.97 (0.49-1.85)		
PLAC/NORX	0.55 (0.29-1.02)	PLAC/NORX	0.58 (0.31-1.07)	PLAC/NORX	0.57 (0.30-1.09)		
IBUIVHIGHDOSE *versus*		IBUIVHIGHDOSE *versus*		IBUIVHIGHDOSE *versus*			
IBUIVCONT	1.19 (0.03-62.65)	IBUIVCONT	1.19 (0.02-83.28)	IBUIVCONT	1.07 (0.02-43.68)		
IBUIV	1.31 (0.29-6.19)	IBUIV	1.14 (0.25-5.07)	IBUIV	1.30 (0.30-5.91)		
PLAC/NORX	0.78 (0.15-4.06)	PLAC/NORX	0.70 (0.15-3.31)	PLAC/NORX	0.77 (0.16-3.87)		
IBUIVCONT *versus*		IBUIVCONT *versus*		IBUIVCONT *versus*			
IBUIV	1.05 (0.03-35.26)	IBUIV	0.95 (0.02-40.48)	IBUIV	1.18 (0.04-54.37)		
PLAC/NORX	0.63 (0.02-21.65)	PLAC/NORX	0.59 (0.01-26.33)	PLAC/NORX	0.69 (0.02-33.84)		
IBUIV *versus*		IBUIV *versus*		IBUIV *versus*			
PLAC/NORX	0.59 (0.33-1.03)	PLAC/NORX	0.62 (0.35-1.11)	PLAC/NORX	0.59 (0.33-1.03)		
Common within-network between-study variance	0.04 (0.00-0.36)	Common within-network between-study variance	0.04 (0.00-0.36)	Common within-network between-study variance	0.04 (0.00-0.36)	Common within-network between-study variance	0.06 (0.00-0.71)
Regression coefficient (log OR scale)	0.013 (-0.142-0.160)	Regression coefficient (log OR scale)	0.000 (-0.001-0.001)	Regression coefficient (log OR scale)	-0.004 (-0.034-0.025)	Regression coefficient (log OR scale)	0.017 (-0.064-0.099)

eTable 42. Meta-regression Analysis Corresponding SUCRA values: Neonatal Mortality

Mean Gestational Age		Mean Birth Weight		Year of Publication		Age of initiation of Treatment	
Treatment	**Mean SUCRA (SD)**	**Treatment**	**Mean SUCRA (SD)**	**Treatment**	**Mean SUCRA (SD)**	**Treatment**	**Mean SUCRA (SD)**
PARAPO	0.67 (0.26)	PARAPO	0.64 (0.27)	PARAPO	0.63 (0.28)	INDOTHERS	0.50 (0.23)
INDOTHERS	0.47 (0.20)	INDOTHERS	0.48 (0.21)	INDOTHERS	0.45 (0.21)	INDOIVCONT	0.39 (0.36)
INDOIVCONT	0.26 (0.29)	INDOIVCONT	0.24 (0.28)	INDOIVCONT	0.27 (0.30)	INDOIV	0.45 (0.20)
INDOIV	0.59 (0.18)	INDOIV	0.57 (0.18)	INDOIV	0.59 (0.18)	IBUPO	0.87 (0.17)
IBUPOHIGHDOSE	0.32 (0.38)	IBUPOHIGHDOSE	0.34 (0.38)	IBUPOHIGHDOSE	0.34 (0.39)	IBUIVCONT	0.53 (0.43)
IBUPO	0.70 (0.20)	IBUPO	0.70 (0.20)	IBUPO	0.71 (0.19)	IBUIV	0.59 (0.21)
IBUIVHIGHDOSE	0.49 (0.34)	IBUIVHIGHDOSE	0.54 (0.35)	IBUIVHIGHDOSE	0.50 (0.34)	PLAC/NORX	0.17 (0.16)
IBUIVCONT	0.55 (0.42)	IBUIVCONT	0.57 (0.42)	IBUIVCONT	0.53 (0.42)		
IBUIV	0.67 (0.19)	IBUIV	0.65 (0.20)	IBUIV	0.69 (0.19)		
PLAC/NORX	0.27 (0.15)	PLAC/NORX	0.26 (0.15)	PLAC/NORX	0.28 (0.16)		

eTable 43. Meta-regression Analysis Results for Outcome: Risk of Necrotizing Enterocolitis

Meta-regression NMA Results For Mean Gestational Age		*Meta-regression NMA Results For Mean Birth Weight*		*Meta-regression NMA Results For Year of Publication*		*Meta-regression NMA Results For Age of Initiation of Treatment*	
Treatment Comparison	**Network Meta-regression OR (95% CrI)**	**Treatment Comparison**	**Network Meta-regression OR (95% CrI)**	**Treatment Comparison**	**Network Meta-regression OR (95% CrI)**	**Treatment Comparison**	**Network Meta-regression OR (95% CrI)**
PARAPO *versus*		PARAPO *versus*		PARAPO *versus*		PARAPO *versus*	
INDOTHERS	0.29 (0.08-1.02)	INDOTHERS	0.27 (0.07-0.91)	INDOTHERS	0.27 (0.08-0.92)	INDOTHERS	0.10 (0.01-0.79)
INDOIVCONT	1.06 (0.20-5.76)	INDOIVCONT	1.03 (0.19-5.65)	INDOIVCONT	0.94 (0.18-5.59)	INDOIVCONT	0.57 (0.04-6.52)
INDOIV	0.45 (0.15-1.32)	INDOIV	0.43 (0.13-1.29)	INDOIV	0.42 (0.14-1.29)	INDOIV	0.32 (0.04-2.36)
IBUPOHIGHDOSE	1.62 (0.23-13.13)	IBUPOHIGHDOSE	1.46 (0.21-11.53)	IBUPOHIGHDOSE	1.47 (0.21-10.29)	IBUPO	0.73 (0.14-3.69)
IBUPO	1.16 (0.44-3.16)	IBUPO	1.12 (0.39-2.99)	IBUPO	1.08 (0.42-2.97)	IBUIVCONT	1.10 (0.07-15.26)
IBUIVHIGHDOSE	0.49 (0.05-4.82)	IBUIVHIGHDOSE	0.43 (0.04-3.88)	IBUIVHIGHDOSE	0.46 (0.05-3.44)	IBUIV	0.42 (0.04-3.30)
IBUIVCONT	1.81 (0.27-14.88)	IBUIVCONT	1.69 (0.25-13.47)	IBUIVCONT	1.70 (0.28-12.97)	PLAC/NORX	0.49 (0.06-3.75)
IBUIV	0.66 (0.22-2.11)	IBUIV	0.65 (0.20-1.98)	IBUIV	0.63 (0.20-2.09)	INDOTHERS *versus*	
PLAC/NORX	0.75 (0.21-2.69)	PLAC/NORX	0.71 (0.19-2.77)	PLAC/NORX	0.72 (0.21-2.53)	INDOIVCONT	5.51 (0.95-32.44)
INDOTHERS *versus*		INDOTHERS *versus*		INDOTHERS *versus*		INDOIV	3.00 (1.31-7.42)
INDOIVCONT	3.54 (0.82-16.15)	INDOIVCONT	3.81 (0.89-16.83)	INDOIVCONT	3.49 (0.80-16.74)	IBUPO	7.02 (2.00-29.92)
INDOIV	1.51 (0.84-2.77)	INDOIV	1.57 (0.90-2.74)	INDOIV	1.54 (0.89-2.78)	IBUIVCONT	10.59 (1.60-78.09)
IBUPOHIGHDOSE	5.44 (0.91-37.59)	IBUPOHIGHDOSE	5.43 (0.90-35.52)	IBUPOHIGHDOSE	5.30 (0.88-34.53)	IBUIV	4.01 (1.38-12.33)
IBUPO	3.92 (1.75-9.10)	IBUPO	4.03 (1.83-9.26)	IBUPO	4.04 (1.80-9.27)	PLAC/NORX	4.64 (1.52-14.91)
IBUIVHIGHDOSE	1.66 (0.23-11.82)	IBUIVHIGHDOSE	1.57 (0.21-12.14)	IBUIVHIGHDOSE	1.68 (0.23-12.04)	INDOIVCONT *versus*	
IBUIVCONT	6.08 (1.14-41.00)	IBUIVCONT	6.20 (1.17-38.04)	IBUIVCONT	6.25 (1.16-43.54)	INDOIV	0.56 (0.12-2.57)
IBUIV	2.25 (1.07-4.94)	IBUIV	2.33 (1.14-5.04)	IBUIV	2.32 (1.07-5.06)	IBUPO	1.30 (0.19-9.64)
PLAC/NORX	2.51 (1.05-6.33)	PLAC/NORX	2.61 (1.07-6.53)	PLAC/NORX	2.66 (1.06-6.77)	IBUIVCONT	1.92 (0.23-17.03)
INDOIVCONT *versus*		INDOIVCONT *versus*		INDOIVCONT *versus*		IBUIV	0.74 (0.18-2.89)
INDOIV	0.42 (0.11-1.68)	INDOIV	0.41 (0.10-1.58)	INDOIV	0.45 (0.11-1.72)	PLAC/NORX	0.85 (0.17-4.41)
IBUPOHIGHDOSE	1.54 (0.17-15.10)	IBUPOHIGHDOSE	1.46 (0.16-12.39)	IBUPOHIGHDOSE	1.51 (0.17-12.82)	INDOIV *versus*	
IBUPO	1.11 (0.26-4.62)	IBUPO	1.07 (0.24-4.54)	IBUPO	1.15 (0.26-4.57)	IBUPO	2.33 (0.65-9.44)
IBUIVHIGHDOSE	0.47 (0.05-4.49)	IBUIVHIGHDOSE	0.41 (0.04-3.71)	IBUIVHIGHDOSE	0.47 (0.05-4.61)	IBUIVCONT	3.46 (0.61-21.64)
IBUIVCONT	1.72 (0.23-15.09)	IBUIVCONT	1.68 (0.21-13.13)	IBUIVCONT	1.80 (0.23-14.99)	IBUIV	1.32 (0.68-2.59)
IBUIV	0.63 (0.17-2.23)	IBUIV	0.63 (0.17-2.14)	IBUIV	0.67 (0.18-2.32)	PLAC/NORX	1.53 (0.70-3.45)
PLAC/NORX	0.71 (0.17-3.20)	PLAC/NORX	0.70 (0.15-2.97)	PLAC/NORX	0.75 (0.17-3.28)	IBUPO *versus*	
INDOIV *versus*		INDOIV *versus*		INDOIV *versus*		IBUIVCONT	1.48 (0.19-12.80)
IBUPOHIGHDOSE	3.65 (0.61-23.87)	IBUPOHIGHDOSE	3.46 (0.62-21.59)	IBUPOHIGHDOSE	3.39 (0.58-20.85)	IBUIV	0.56 (0.14-2.23)
IBUPO	2.62 (1.34-5.29)	IBUPO	2.58 (1.34-5.13)	IBUPO	2.60 (1.31-5.19)	PLAC/NORX	0.66 (0.17-2.47)
IBUIVHIGHDOSE	1.11 (0.16-7.34)	IBUIVHIGHDOSE	1.00 (0.14-7.39)	IBUIVHIGHDOSE	1.08 (0.15-7.41)	IBUIVCONT *versus*	
IBUIVCONT	4.06 (0.82-24.84)	IBUIVCONT	3.96 (0.80-22.86)	IBUIVCONT	3.98 (0.82-25.51)	IBUIV	0.38 (0.07-1.87)
IBUIV	1.50 (0.86-2.57)	IBUIV	1.50 (0.90-2.61)	IBUIV	1.49 (0.85-2.59)	PLAC/NORX	0.45 (0.07-2.73)
PLAC/NORX	1.68 (0.79-3.55)	PLAC/NORX	1.66 (0.81-3.53)	PLAC/NORX	1.70 (0.81-3.62)	IBUIV *versus*	
IBUPOHIGHDOSE *versus*		IBUPOHIGHDOSE *versus*		IBUPOHIGHDOSE *versus*		PLAC/NORX	1.16 (0.53-2.62)
IBUPO	0.72 (0.13-3.61)	IBUPO	0.75 (0.14-3.81)	IBUPO	0.76 (0.15-3.90)		
IBUIVHIGHDOSE	0.31 (0.02-3.52)	IBUIVHIGHDOSE	0.29 (0.02-3.27)	IBUIVHIGHDOSE	0.32 (0.02-3.74)		
IBUIVCONT	1.12 (0.10-12.50)	IBUIVCONT	1.15 (0.11-13.03)	IBUIVCONT	1.21 (0.11-14.20)		
IBUIV	0.41 (0.06-2.35)	IBUIV	0.43 (0.07-2.51)	IBUIV	0.44 (0.07-2.50)		
PLAC/NORX	0.46 (0.07-2.82)	PLAC/NORX	0.48 (0.07-2.89)	PLAC/NORX	0.50 (0.08-3.11)		
IBUPO *versus*		IBUPO *versus*		IBUPO *versus*			
IBUIVHIGHDOSE	0.43 (0.06-2.95)	IBUIVHIGHDOSE	0.38 (0.05-2.75)	IBUIVHIGHDOSE	0.42 (0.06-2.82)		
IBUIVCONT	1.55 (0.30-9.83)	IBUIVCONT	1.52 (0.30-9.33)	IBUIVCONT	1.55 (0.29-10.41)		
IBUIV	0.57 (0.28-1.15)	IBUIV	0.58 (0.29-1.15)	IBUIV	0.58 (0.28-1.14)		
PLAC/NORX	0.64 (0.28-1.45)	PLAC/NORX	0.64 (0.28-1.46)	PLAC/NORX	0.66 (0.28-1.49)		
IBUIVHIGHDOSE *versus*		IBUIVHIGHDOSE *versus*		IBUIVHIGHDOSE *versus*			
IBUIVCONT	3.68 (0.33-47.36)	IBUIVCONT	4.02 (0.39-50.24)	IBUIVCONT	3.68 (0.35-46.45)		
IBUIV	1.34 (0.22-8.78)	IBUIV	1.49 (0.24-10.33)	IBUIV	1.37 (0.21-9.41)		
PLAC/NORX	1.50 (0.22-10.76)	PLAC/NORX	1.65 (0.23-13.45)	PLAC/NORX	1.60 (0.23-12.08)		
IBUIVCONT *versus*		IBUIVCONT *versus*		IBUIVCONT *versus*			
IBUIV	0.37 (0.06-1.66)	IBUIV	0.38 (0.07-1.66)	IBUIV	0.38 (0.06-1.71)		
PLAC/NORX	0.41 (0.06-2.20)	PLAC/NORX	0.42 (0.07-2.10)	PLAC/NORX	0.43 (0.06-2.16)		
IBUIV *versus*		IBUIV *versus*		IBUIV *versus*			
PLAC/NORX	1.12 (0.55-2.35)	PLAC/NORX	1.11 (0.54-2.29)	PLAC/NORX	1.15 (0.55-2.33)		
Common within-network between-study variance	0.05 (0.00-0.45)	Common within-network between-study variance	0.04 (0.00-0.46)	Common within-network between-study variance	0.04 (0.00-0.44)	Common within-network between-study variance	0.05 (0.00-0.73)
Regression coefficient (log OR scale)	-0.022 (-0.192-0.143)	Regression coefficient (log OR scale)	0.000 (-0.001-0.001)	Regression coefficient (log OR scale)	0.003 (-0.039-0.048)	Regression coefficient (log OR scale)	0.008 (-0.086-0.106)

eTable 44. Meta-regression Analysis Corresponding SUCRA values: Risk of Necrotizing Enterocolitis

Mean Gestational Age		Mean Birth Weight		Year of Publication		Age of initiation of Treatment	
Treatment	**Mean SUCRA (SD)**	**Treatment**	**Mean SUCRA (SD)**	**Treatment**	**Mean SUCRA (SD)**	**Treatment**	**Mean SUCRA (SD)**
PARAPO	0.61 (0.25)	PARAPO	0.64 (0.24)	PARAPO	0.64 (0.24)	PARAPO	0.75 (0.29)
INDOTHERS	0.06 (0.09)	INDOTHERS	0.06 (0.08)	INDOTHERS	0.06 (0.09)	INDOTHERS	0.01 (0.05)
INDOIVCONT	0.63 (0.27)	INDOIVCONT	0.64 (0.27)	INDOIVCONT	0.61 (0.28)	INDOIVCONT	0.57 (0.29)
INDOIV	0.20 (0.11)	INDOIV	0.21 (0.11)	INDOIV	0.21 (0.11)	INDOIV	0.27 (0.16)
IBUPOHIGHDOSE	0.76 (0.27)	IBUPOHIGHDOSE	0.75 (0.28)	IBUPOHIGHDOSE	0.74 (0.28)	IBUPO	0.68 (0.23)
IBUPO	0.72 (0.14)	IBUPO	0.71 (0.15)	IBUPO	0.71 (0.15)	IBUIVCONT	0.79 (0.25)
IBUIVHIGHDOSE	0.33 (0.32)	IBUIVHIGHDOSE	0.30 (0.31)	IBUIVHIGHDOSE	0.32 (0.31)	IBUIV	0.43 (0.17)
IBUIVCONT	0.80 (0.24)	IBUIVCONT	0.80 (0.24)	IBUIVCONT	0.80 (0.24)	PLAC/NORX	0.51 (0.20)
IBUIV	0.41 (0.14)	IBUIV	0.42 (0.13)	IBUIV	0.41 (0.14)		
PLAC/NORX	0.48 (0.19)	PLAC/NORX	0.48 (0.19)	PLAC/NORX	0.49 (0.19)		

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