Supplement 2. Summary of changes between published protocol and manuscript

Sections	Published Protocol	Final systematic review manuscript	Reasons for the changes
Type of study	"We will include RCTs and quasi-RCTs"	The review only included RCTs	To improve the quality of evidence generated from synthesis of results
Overall risk of bias assessment for the individual outcomes for each study	Not specified	The overall RoB for each study was assessed by taking the average of the following RoB items: sequence generation, allocation concealment and blinding	Prior to data extraction, it was decided by expert consensus that the aforementioned RoB items provided the most robust assessment of the overall RoB given the nature of the population, interventions and outcomes involved in the RCTs included this systematic review
Primary outcome measure	"Failure of permanent PDA closure" defined as failure to close the PDA	"PDA closure" defined as closure of an hs-PDA within a week of administration of the first dose of the intervention	We intended to depict the primary effectiveness outcome as a positive outcome to make it easier for the readers to interpret
Secondary outcome assessment	3 effectiveness and 11 safety outcomes were initially planned for evaluation	Quantitative synthesis of data was conducted with eight outcomes, that included all three effectiveness outcomes and five safety outcomes. The outcomes that were not explored included the following: severe intra-ventricular hemorrhage; periventricular leukomalacia; neurodevelopmental disability; intestinal perforation; gastrointestinal bleeding; time to full enteral feeds	Paucity of data

Supplement 2. Summary of changes between published protocol and manuscript (…continued)			
Sections	**Published Protocol**	**Final systematic review manuscript**	**Reasons for the changes**
Secondary outcome definitions	• Mortality: Death during the first 28 days of life • Reopening of the ductus arteriosus: Number of neonates with echocardiographically determination of reopening of the ductus • Chronic lung disease (CLD): Total number of neonates with oxygen requirement at 28 days postnatal age in addition to compatible clinical and roentgenographic findings. • Necrotizing enterocolitis (NEC): Number of neonates with NEC (any stage)	• Mortality: Death at 36 weeks' postmenstrual age or before discharge • Need for repeat pharmacotherapy: Number of neonates who require a repeat course of pharmacotherapy following an initial course for treatment of a persistent hs-PDA • Bronchopulmonary dysplasia (BPD): Number of neonates who require oxygen at 36 weeks' postmenstrual age • Necrotizing enterocolitis (NEC): Number of neonates with NEC (stage 2 or higher based on Bell criteria).	The definitions of some of the secondary outcomes were modified to make them more clinically relevant to clinicians and decision makers based on consensus from experts
Network Plots	Possibility of combination of multiple treatment modalities into single nodes were not discussed in the protocol	Several variations of indomethacin that are seldom used in the current context, namely, indomethacin with furosemide, indomethacin with dopamine, high dose IV indomethacin, prolonged infusion of IV indomethacin, oral indomethacin and echocardiography-guided indomethacin infusion were condensed into a single node named 'Indomethacin, other types' (INDOTHERS). Similarly, placebo and no treatment were combined into a single node named 'Placebo/No Treatment' (PLAC_NORx). Hence the final NMA was conducted with 10 nodes, each depicting a treatment modality	To make the results more relevant in the current clinical context and for ease of analysis

Supplement 2. Summary of changes between published protocol and manuscript (…continued)			
Sections	**Published Protocol**	**Final systematic review manuscript**	**Reasons for the changes**
Exploring heterogeneity	"We propose, a priori, the following potential sources of heterogeneity, which could be possible effect modifiers: gestational age (<28; 28–32; >32 weeks of gestational age), birth weight (<1000; 1000–1500; >1500 g), different doses of the interventions, time of administration of the first dose of the intervention (<3, 3–7, >7 days), echocardiographic findings (PDA size and left atrium:aortic root ratio), time of PDA assessment post pharmacotherapy (<24 hours, 24 hours to 3 days, and >7 days) and previous medical PDA medical therapy."	The sources of heterogeneity that were explored included: gestational age (GA) (as a continuous variable); birth weight (BW) (as a continuous variable); time of administration of first dose (as a continuous variable).	We conducted a network meta-regression analysis (instead of subgroup analysis) using GA, BW and time of initiation of treatment as potential effect modifiers, hence we chose to use continuous measures. Timing of PDA closure assessment was not explored due to paucity of data. Variation in echo findings were not included in the model as the studies were fairly uniform in their echo definition of hs-PDA