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Cost-effectiveness Analysis of Ibuprofen versus Indomethacin or Paracetamol for the Treatment of Patent Ductus Arteriosus in Preterm Neonates

BY

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ABSTRACT

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Title: Cost-effectiveness Analysis of Ibuprofen versus Indomethacin or Paracetamol for the Treatment of Patent Ductus Arteriosus in Preterm Neonates

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Objective: This thesis sought to evaluate the cost-effectiveness of oral paracetamol and intravenous (IV) indomethacin as alternatives to ibuprofen for patent ductus arteriosus (PDA) in neonates in Hamad Medical Corporation (HMC), Qatar.

Methods: Decision-analytic, literature-based, economic simulation models were constructed, from the hospital perspective, to evaluate oral/IV ibuprofen versus IV indomethacin, and oral/IV ibuprofen versus oral paracetamol, as first-line therapies for PDA closure. Cost model inputs were HMC based, and therapy success was defined as PDA closure with/without adverse events.

Results: Oral ibuprofen is dominant/cost-effective over IV indomethacin in 92% of simulated cases, but oral paracetamol was 82% dominant/cost-effective over oral ibuprofen. Against IV ibuprofen, IV indomethacin was 59% dominant/cost-effective, whereas oral paracetamol was dominant/cost-effective in 91% of the cases. Sensitivity analyses confirmed the study's robustness.

Conclusion: For PDA closure, while IV indomethacin was cost-effective against IV ibuprofen, oral paracetamol was cost-effective against both oral and IV ibuprofen.

DEDICATION

To my parents,

for always supporting me.

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ABBREVIATIONS

AE	Adverse event
AWH	Al Wakrah hospital
BPD	Bronchopulmonary dysplasia
BW	Body weight
CBA	Cost-benefit analysis
CDSR	Cochrane database of systematic reviews
CEA	Cost-effectiveness analysis
CI	Confidence interval
CLD	Chronic lung disease
CMA	Cost minimization analysis
CNS	Central nervous system
COX	Cyclooxygenase
CSF	Cerebrospinal fluid
CUA	Cost-utility analysis
DA	Ductus arteriosus
DCER	Decremental cost-effectiveness ratio
ELBW	Extremely low birth weight
FDA	Food and drug administration
FiO_2	Fraction of inspired oxygen
GA	Gestational age
GDP	Gross domestic product
GIB	Gastrointestinal bleeding

GM	Germinal matrix
HCUP	Health care cost and utilization product
HMC	Hamad Medical Corporation
HRQOL	Health related quality of life
HSCRC	Health service cost review commission
HSPDA	Hemodynamically significant patent ductus arteriosus
ICER	Incremental cost-effectiveness ratio
ICROP	International classification of retinopathy of prematurity
IRB	Institutional review board
IV	Intravenously
IVH	Intraventricular hemorrhage
MA	Meta-analysis
MRI	Magnetic resonance imaging
MRC	Medical Research Center
MD	Mean difference
NMAS	Network meta-analyses
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NPO	Nothing by mouth
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PDA	Patent ductus arteriosus
PGE_2	Prostaglandin E_2

PGG_2	Prostaglandin G_2
PGI_2	Prostaglandin I_2
PHCC	Primary Healthcare Corporation
PMA	Postmenstrual age
PaO_2	Partial pressure of oxygen
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PVL	Periventricular leukomalacia
PVR	Pulmonary vascular resistance
P&T	Pharmacy and therapeutics
QALY	Quality-adjusted life years
QAR	Qatari riyal
QOL	Quality of life
RCT	Randomized clinical trial
RDS	Respiratory distress syndrome
ROBIS	Risk of bias in systematic review
ROD	Retinopathy of prematurity
RR	Relative risk
SR	Systematic review
SUCRA	Surface under the cumulative ranking curve
UK	United Kingdom
US	Ultrasound
USA	United States of America
VLBW	Very low birth weight

WHO	World Health Organization
WTP	Willingness-to-pay
WWRC	Women Wellness and Research Center

CHAPTER 1: INTRODUCTION

Patent Ductus Arteriosus (PDA)

During embryonic development, the lower part of the proximal descending aorta is connected to the top portion of the left pulmonary artery via a vascular structure known as ductus arteriosus (DA), presented in Figure 1.1 (1). This functions to divert blood away from the main pulmonary artery and into the aorta, allowing blood to bypass circulation to the non-functional fetal lungs. However, after birth, the opening of the fetal vessel is no longer required, and the DA constricts spontaneously during the first three days of life and eventually obliterates. It is necessary for the DA to rapidly close after birth for the vascular transition to the mature double circulation. A patent ductus arteriosus (PDA) is a congenital condition where the DA fails to close post-delivery and remains patent or, in other words, "open". The physiological consequences of the PDA, and the significance of its therapy, depend primarily on the scale of the PDA (2). PDA can be diagnosed as "silent" (clinically not visible), minimal, moderate, or large.

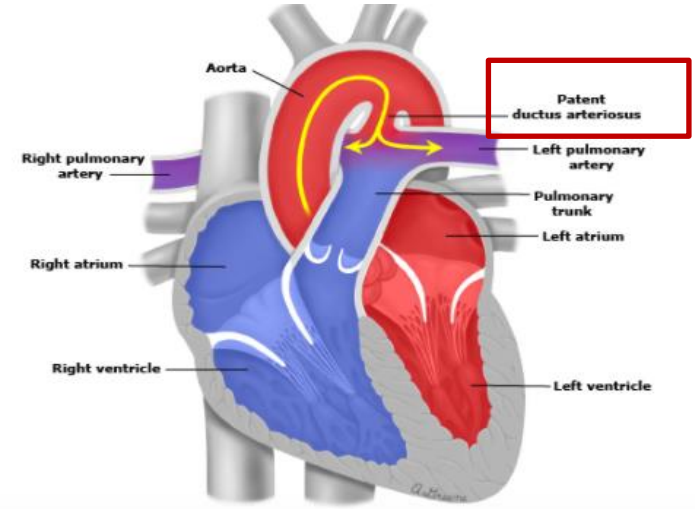

Figure 1.1. Blood flow with ductus arteriosus

Fetal Ductal Circulation

The fetal blood circulation is distinctive from the after-birth circulation, whereby the placenta functions as the fetal lungs. The oxygen-rich blood passes from the placenta into the umbilical vein, where it passes through the fetal liver and into the right side of the heart (3). In the heart of the fetus, the right ventricles constitute 65% of the cardiac output, where only 5-10% passes through the pulmonary artery to the lungs (2). The fetal lungs are occupied with amniotic fluid and, therefore, do not engage in gas exchange. The presence of low systemic arterial oxygen tension allows the fetus to maintain a high pulmonary vascular resistance (PVR) by constricting the pulmonary vasculature known as hypoxic pulmonary vasoconstriction, restricting the amount of blood flow (4). This is a protective reflex mechanism allowing the circulation to divert away from the hypoxic areas of the lungs and towards the placenta. In contrast, during hypoxemia, the systemic circulation dilates, creating a low systemic vascular resistance (4). The systemic circulation receives 40% of the cardiac output leading to low systemic pressure compared to the fetal lungs, which are fluid-filled, causing high PVR. Two significant right-to-left shunting occurs in the fetal blood circulation due to high pulmonary and low systemic vascular resistance, as illustrated in Figure 1.2 (1):

1. Oxygenated blood is shunted from the right to the left atrium through the oval foramen.
2. About 90% of the blood in the right ventricle flowing into the pulmonary artery is shunted across to the descending aorta through the DA.

The low oxygen pressure preserves the patency of the fetal circulation structure by inducing pulmonary vascular constriction, causing high resistance, thereby facilitating right-to-left shunting through the ductus arteriosus and towards the placenta for

oxygenation. This fetal structure is, therefore, essential for the normal development of the fetus (1). Another factor that controls the patency of DA is the cyclooxygenase-mediated products, primarily prostaglandin E_2 (PGE_2) and prostaglandin I_2 (PGI_2) of arachidonic acid metabolism. PGE_2 and PGI_2 are locally produced in the placenta in high levels and are present in the vascular tissues causing vasodilation of the DA through interaction with prostanoid receptors of the ductus (2).

The transition from Fetal Circulation to Neonatal Circulation

At birth, when the umbilical cord is clamped, significant cardiopulmonary adaptations occur, which aids in the transition of gas exchange from the placenta to the lungs. A major shift in vascular pressure occurs in the neonate as it separates from the placenta.

First, the PVR is reduced due to clearance of the alveolar fluid and the increase in the arterial partial pressure of oxygen (paO_2) as the lung expands with the first breath of air. Simultaneously, as the supply of the low-pressure placenta is removed, the systemic vascular resistance increases (5). These changes in vascular pressure reduce the right-to-left shunting through the DA, shifting to left-to-right shunting associated with an increase in oxygen saturation. The sudden increase in oxygen content restrains the smooth muscle potassium-dependent channels of the ductus, leading to an influx of calcium causing constriction of the ductus (6).

Second, the drop in the levels of circulating PGE_2 and PGI_2 due to the elimination of the placenta causes contraction of the medial smooth muscle fibers in the DA, resulting in thicker walls and the narrowing of the lumen of the vessel (2, 6). As a result, the inner walls of the ductus develop relative ischemia, leading to a formation of vascular endothelial growth factor that stimulates endothelial cell proliferation in the intima, occluding the lumen of the duct that turns into a non-

contractile ligament. In term neonates, complete functional closure occurs in a period of 24 to 48 hours of birth, while complete anatomic closure occurs in 2 to 3 weeks, where the resulting sealed fibrous band persists; known as ligamentum arteriosum, Figure 1.2 (7).

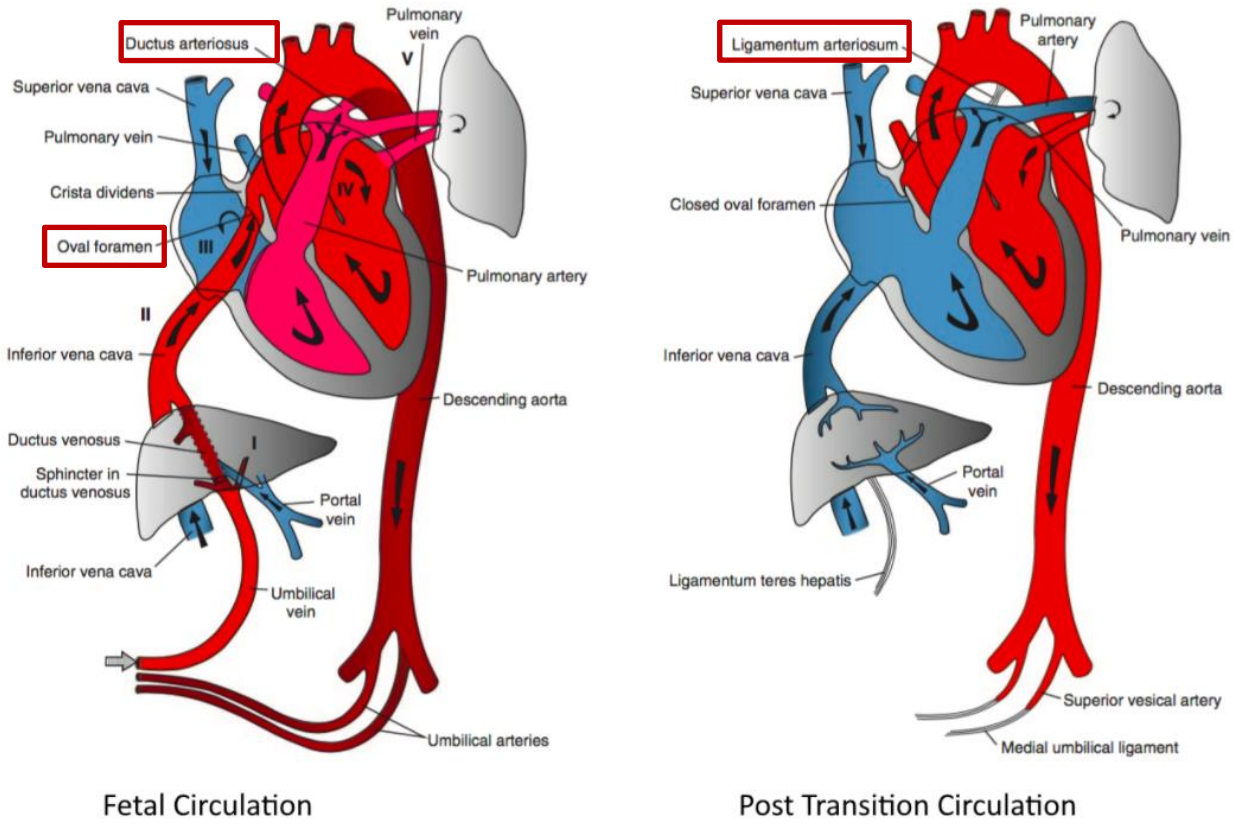

Figure 1.2. Difference between intrauterine and extrauterine circulation

Pathophysiology of PDA

During the preterm stages of infancy, the DA is highly sensitive to endogenous vasodilators, such as prostaglandin (PG) and nitric oxide, which keeps the vessel patent. However, at full-term gestational age (GA), the ductus becomes mature and develops more oxygen sensitivity than PGs. Therefore, in the presence of high PaO_2, in term neonates, the DA undergoes constriction and complete closure. However, in preterm neonates, the DA, being insufficiently mature, fails to constrict and close after birth. Even in those preterm infants that achieve constriction of the

DA, the DA is less likely to become severely ischemic, which is required to initiate the remodeling mechanism, essential for complete obliteration of the lumen to ensure absolute elimination of nutrient flow to the vessel wall (8, 9).

As a result, left-to-right shunting of blood occurs from the higher pressure of blood in the aorta to the lower pressure of blood in the pulmonary artery through the open DA. This has two main consequences (10):

1. Pulmonary over circulation: increased blood flow to the lungs leading to an increase in pulmonary venous pressure, which can contribute to pulmonary edema and hemorrhage in severe cases.
2. Reduced systemic blood flow: the systemic blood flow is redirected towards the lungs as the PVR is lower than the systemic vascular resistance, leading to the concept of "ductal steal".

Based on the degree of left-to-right shunting, PDA can be associated with many neonatal morbidities. The low systemic perfusion can lead to ischemic injury to the brain that results in periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH) within 72 hours after birth, ischemia of the gut that can cause necrotizing enterocolitis (NEC), presenting five days after delivery, and reduced renal perfusion that causes acute kidney injury. In preterm infants, PDA can be hemodynamically significant (symptomatic) or hemodynamically insignificant (silent) (10).

However, there is no universally approved and validated PDA severity classification to correlate clinical signs with echocardiographic features or laboratory findings. The cardiologist must determine if a PDA leads to end-organ hypoperfusion and compromise. Within this context, a "hemodynamically significant PDA" (hsPDA) is characterized as a PDA with significant left-to-right shunting of blood as associated

by a DA diameter of ≥1.5 mm, a left atrium/aortic root diameter ratio of ≥1.5:1, and an inverted diastolic blood flow in the descending aorta and renal arteries (11).

Epidemiology of PDA in Neonates

In term infants, the incidence of isolated PDA, defined as persisting PDA up to or beyond six weeks after delivery, ranges from 3 to 8 per 10,000 live births. It accounts for 5% - 10% of all congenital heart diseases (12, 13). However, the incidence surges up to 60% in preterm infants and is inversely related to gestational age and birth weight. In infants with very low birth weight (VLBW) (1000 – 1500 g), 30% experienced persistent PDA, while the number increases to 55% in extremely low birth weight infants (ELBW) (<1000 g) (13, 14, 15). Although the ductal shunt might close spontaneously, at least 60% of extremely preterm newborns (before 28 weeks of pregnancy) will require surgical or medical treatment (16, 17). No firm statistics exist regarding mortality associated with PDA; however, a single-center cohort study conducted in Denmark showed a three-fold increase in odds of mortality or severe morbidity in extremely preterm neonates on day three compared to infants without PDA (18). Additionally, it is estimated that, if left untreated, the mortality rate of PDA is 20% by age 20 years, 42% by age 45 years, and this increases to 60% by age 60 years (13).

In Qatar, the Hamad Medical Corporation (HMC), i.e. the leading healthcare provider in the country, reported that one in every 10 newborns was premature and that different neonatal intensive care units (NICUs) in various hospitals under HMC cared for 4200 babies born prematurely from January 2018 till September 2019 (19). No statistics are available in Qatar regarding the prevalence or incidence of PDA, but a descriptive retrospective chart review study conducted in the main tertiary NICU of HMC, from January 2003 to December 2007, illustrated that 82 preterm neonates

were diagnosed with PDA out of 147 infants (20). A total of 63 infants (76%) required medical intervention and, of this, 20 infants required surgical ligation after the failure of initial pharmacologic treatment. The overall spontaneous closure, including those who failed to respond to the initial medical treatment, was 39% (20). These relatively high numbers require close attention from authorities, research centers, and healthcare providers in order to ensure that this population is receiving optimal care.

Complications of Hemodynamically Significant PDA

In neonates with ELBW (<1000 g) and VLBW (<1500 g), lung injury is frequently combined with myocardial malfunction due to the pulmonary over circulation, causing volume overload along with the concept of ductal steal and, ultimately, causing diminished systemic perfusion (21). Thus, preterm neonates born with birth weight <1000 g are prone to vital organ hypo-perfusion, consequently causing additional morbidities such as NEC, IVH, PVL, bronchopulmonary dysplasia (BPD), and renal failure. Although hsPDA is associated with increased mortality and morbidity, it has not been proven to be causative of them as these can also occur as a consequence of prematurity (10).

Necrotizing Enterocolitis

NEC is the most prevalent acute gastrointestinal emergency in preterm neonates in the NICU. The pathological mechanism of NEC is about the intestinal ischemia of the terminal ileum or colon. This is usually marked by abdominal distension, bloody stools, and intestinal pneumatosis (22). The true incidence of NEC is uncertain due to inconsistencies in published studies, specifically, the prevalence of suspected NEC (stage I). Although this is suspected in around one-third of cases, it is not reported in most studies (22). The management of stage I NEC involves

supportive care and intensive diagnostic evaluation. As the disease advances to stage II, medical antibiotic treatment is used. Management requiring surgical intervention is only indicated when perforation of the intestine occurs in stage IIIB (23).

NEC can be multifactorial. It, however, occurs in more than 90% of cases in neonates with body weight (BW) <1500 g (very low birth weight) and GA of <32 weeks (24). The incidence of preterm infants with GA <32 weeks varies within 2-7.5% in the NICU worldwide. This rate increases by five-fold for infants with BW <1000 g, born before 28 weeks of gestation (22). The risk of mortality in infants with NEC ranges from 15-30%, which is inversely related to GA and BW.

The clinical diagnosis of NEC is based on the presence of clinical and radiologic signs, which can be challenging to identify in the early stages. In 1978, Dr Martin Bell developed criteria based on clinical and radiologic signs known as Bell staging criteria, which Dr Robert Kleigman modified in 1979 and 1986 (25, 26). The current standard for diagnosing, staging, and treatment of NEC is the modified Bell staging.

Table 1.1. Bell Staging Criteria for Necrotizing Enterocolitis (NEC)

Stage			**Clinical signs**	**Treatment**
I.	**Suspected NEC**	A	Temperature instability, bradycardia	NPO, antibiotics Three days
		B	Same as IA	Same as IA
II.	**Definite NEC**	A: Mildly ill	Same as I	NPO, antibiotics 7-10 days
		B: Moderately ill	Same as I + metabolic acidosis	NPO, antibiotics 14 days
III.	**Advanced NEC**	A: Severely ill	Same as IIB + hypotension, neutropenia, respiratory acidosis	NPO, antibiotics 14 days, fluid resuscitation
		B: Severely ill	Same as IIIA	Same as IIIA, surgery

NPO: Nothing by mouth

Intraventricular Hemorrhage

IVH is the most frequent form of acute central nervous system (CNS) complications in preterm infants. It is intracranial bleeding initiated in the paraventricular subependymal germinal matrix (GM) and can extend to the lateral ventricular system. The GM is an area of active neuronal proliferation where there is a rich vasculature (27). It is prevalent in premature infants with a BW of less than 1500 g, where the overall incidence of IVH is 18-25%, and 90% of the cases appear in the first three days (28). Male neonates are at a higher risk of developing IVH and more severe grades compared to females (27). Using ultrasound (US) and clinical examination can help diagnose IVH. In 1978, the first classification approach for IVH was developed by Papile et al., based on computerized tomography to categorize IVH (29). The severity of IVH is graded according to the grading system of Papile et al. or Volpe (29, 30). The I and II grading scores involve less hemorrhage, while the III and IV grades are considered severe, with a mortality rate of 20-50% (31). The lower grade of IVH resolves spontaneously over days to weeks, while about 20% and 40% of grade 3 and grade 4 require shunting (27, 32). The consequences of IVH in preterm infants involves adverse neurodevelopmental effects such as seizures, motor deficits, deafness, blindness, and cognitive impairment. Neonates born before 28 weeks with grade I-II IVH were twice as likely to develop moderate to severe neurosensory impairment (22%) in comparison to those without IVH (12%), while neonates with grade III-IV had the highest rate of 43% (33).

Table 1.2. Papile Grading Criteria for Intraventricular Hemorrhage (IVH)

Grade (Incidence)	Papile criteria	Volpe criteria	Treatment
I (40%)	Hemorrhage only in the germinal matrix	Blood in the germinal matrix with/without IVH <10% of ventricular space	No therapy
II (25%)	Hemorrhage extend to the lateral ventricles without ventricular dilation	IVH occupying 10-50% of ventricular space	No therapy
III (20%)	Blood in the lateral ventricles leading to enlargement	IVH occupying >50% with/without ventricular echo-densities	Ventriculoperitoneal shunt
IV (15%)	Extension of hemorrhage into brain white matter parenchyma	Periventricular hemorrhagic infarction	Ventriculoperitoneal shunt

Periventricular Leukomalacia

The softening of white brain tissue around the ventricles is known as PVL. In the brain, the ventricles are fluid-filled chambers that hold the cerebrospinal fluid (CSF). This white matter transfers signals from one part of the brain to another through nerve cells and the spinal cord. PVL is caused by a loss of blood supply to the brain tissue before, during, or after birth leading to damaged or dead brain tissue (34). It is the most common ischemic brain damage in neonates born prematurely, specifically before 32 weeks of GA, due to the fragile anatomical features. One systematic review identified the incidence of PVL in preterm neonates to be 39.6% under 28 weeks of gestation, 27.4% under 32 weeks of gestation, and 7.3% under 37 weeks of gestation (35). This can be diagnosed using US and magnetic resonance imaging (MRI) tests. There is no particular therapy to cure PVL, and neonates will require regular follow-up with physical, occupational, and speech therapists. Possible complications of PVL can

be physical and mental, where, in severe cases, this can lead to serious developmental delays or cerebral palsy (34).

Bronchopulmonary Dysplasia

BPD is a serious chronic lung disease that majorly affects premature infants. It is also referred to as chronic lung disease (CLD) of infancy. It occurs in infants with respiratory distress syndrome (RDS) that require supplemental oxygen after 28 days of age or mechanical ventilation in premature infants after 36 weeks of postmenstrual age (PMA). Exposure to the prolonged treatment of supplemental oxygen and invasive respiratory support contributes to chronic lung injury in preterm infants. The incidence of BPD in premature infants born at 22 weeks of gestation and those born at 28 weeks of gestation ranged from 85% to 23%, respectively. The incidence and severity of BPD are inversely proportional to the infant's BW and GA, where neonates born after 30 weeks of gestation rarely develop BPD (36). The grading of BPD is based on the fraction of inspired oxygen (FiO_2) required by infants, reflecting the concentration of oxygen in the mixture of gases. A gas mixture at room air has a FiO_2 of 21%, which means that the oxygen concentration at room air is 21% (37). The different stages of BPD based on the need for FiO_2 are represented in Figure 1.3.

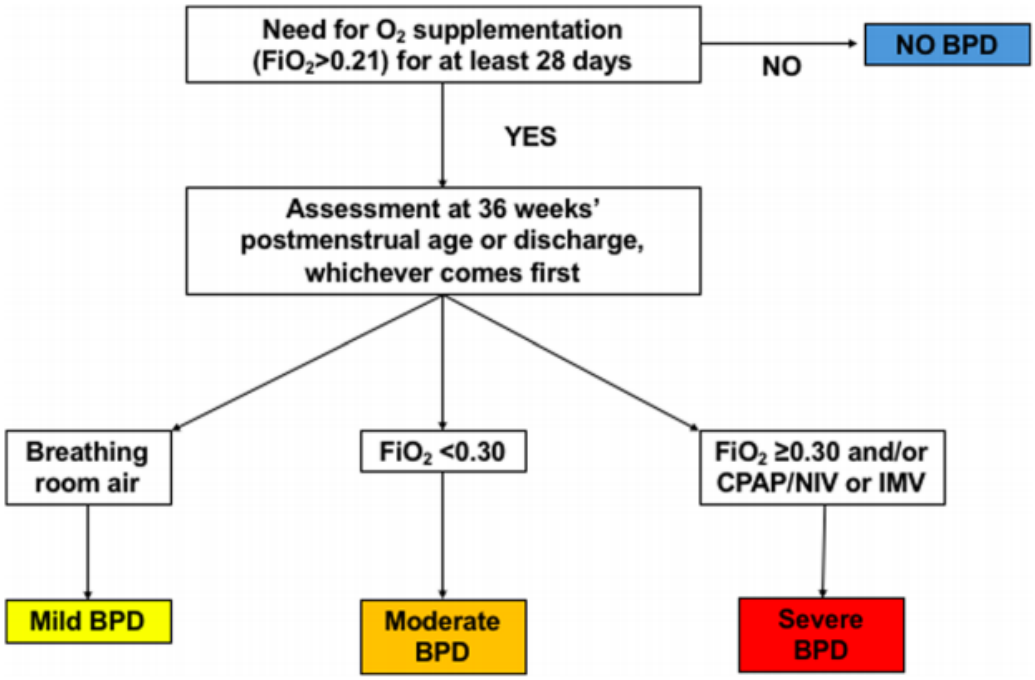

Figure 1.3. Grade of bronchopulmonary dysplasia (BPD)

Retinopathy of Prematurity

In preterm babies, retinopathy of prematurity (ROP) is a developmental vascular proliferative disease that affects the retina due to inadequate retinal vascularization. Prematurity is the most significant risk factor for developing ROP, where the incidence and severity of ROP increase with a decrease in GA and BW of neonates (38).

A population-based cohort study from New Zealand and Australia has found an elevated prevalence of severe ROP with decreased GA. The incidence of severe ROP was observed in 10% of neonates born at <32 weeks of GA, where it was suggested that neonates born ≥32 weeks are at low risk of developing ROP (39). The severity of ROP is classified based on the international classification of ROP (ICROP), first published in 1984 to standardize the terminology used to describe

ROP. In 2005, the ICROP was revised by the second committee of ROP classification (40). The classification of ROP is based on four categories (38, 41): (i) the location of the disease relative to the optic nerve is described by its zone, typically written using roman numerals as illustrated in Figure 1.4 (38), (ii) the degree of severity is defined as stages, described in Table 1.3 (38), (iii) the presence or absences of dilated and tortuous posterior pole vessels know as plus disease, and (iv) the degree of the disease described using clock hours.

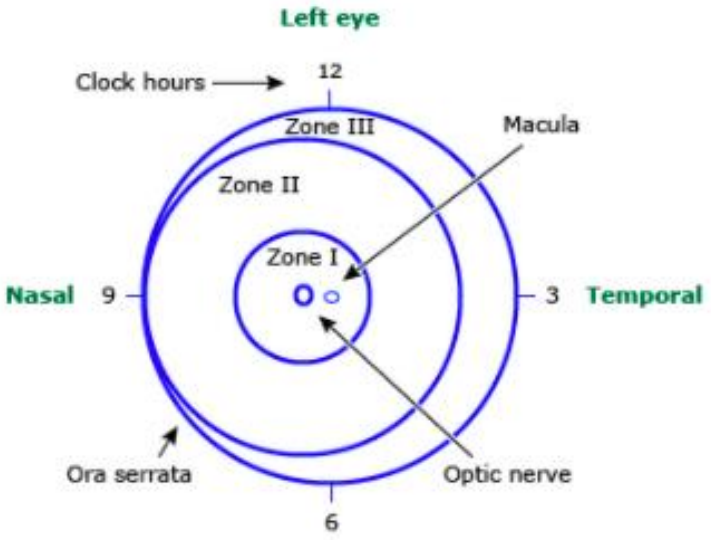

Figure 1.4. International classification of retinopathy of prematurity (ICROP)

Table 1.3. International Classification of Retinopathy of Prematurity

Zone	
Zone I	The central zone at the posterior pole of the eye with the optic nerve
Zone II	Circle outside zone I with a radius from the optic nerve to the nasal ora serrata
Zone III	The remaining outer temporal crescent of the retina
Stage	
Stage 1	A flat white line that demarcates the vascular and avascular retina
Stage 2	A ridge of fibrous tissue protrudes into the vitreous
Stage 3	New blood vessels and fibrous tissue grow along the ridge
Stage 4	Partial retinal detachment
4A	Exclude the macula
4B	Includes the macula
Stage 5	Total retinal detachment

Management of PDA

Conservative Management

Infants diagnosed with hsPDA, who weigh more than 1000 g at birth, can be managed successfully using a conservative approach of measurement. The general conservative measures include (i) moderate fluid restriction between 120-130 mL/kg with proper nutrition of at least 120 kcal/kg/day, (ii) respiratory support using a positive expiratory pressure to ensure adequate oxygen (target 90-95%), and (iii) a neutral thermal environment to minimize the demands of the left ventricles (42).
In neonates with PDA, who are at a higher risk or with a BW of less than 1000 g, conservative management is recommended before initiating pharmacological therapy.

Generally, treatment is not initiated in the first few days of birth, as there is an increase in PVR. However, pharmacotherapy is considered within the second week if conservative management fails to control hsPDA measures, such as pulmonary edema (43).

Pharmacological Closure

A pharmacological course is initiated in neonates who are still on mechanical ventilation a week after birth and have confirmed hsPDA with echocardiography (42). There are three pharmacological options available for PDA constriction: indomethacin, ibuprofen, and paracetamol (acetaminophen) (42,43). Indomethacin and ibuprofen are nonsteroidal anti-inflammatory drugs (NSAIDS) that non-selectively inhibit cyclo-oxygenase (COX) enzymes to reduce levels of PGs, which maintains the patency of the DA. The initial step for PG production is the release of arachidonic acid from the phospholipids of the cell membrane using the enzymatic activity of phospholipase. By COX, the free arachidonic acid is converted to prostaglandin G_2 (PG G_2). This is followed by a peroxidase reaction that is also catalyzed by the COX enzyme, usually found in various tissues, known as COX-1. The PG G_2 is converted to prostaglandin H_2 (PG H_2), where tissue-specific isomerases transform it to other PGs. In vascular tissues, such as the DA, the endothelial cells express PG E_2 and PG I_2. PG E_2 is an essential mediator responsible for maintaining the tone of the smooth muscle of the DA (44).

In comparison, paracetamol reduces the synthesis of PG through a different mechanism than COX. Although the latest randomized controlled trials (RCTs) indicate its efficacy for the closure of PDA, paracetamol approval for this indication is still pending by the Food and Drug Administration (FDA). Paracetamol is administered in neonates when a non-selective COX inhibitor is contraindicated. The

choice of non-selective COX inhibitor for treatment is majorly dependent on the hospital. After completing a course of treatment, an echocardiogram is performed following 24-48 hours to ensure the positive response (i.e., PDA closure) (43).

Surgical Ligation

Surgical ligation is reserved for neonates with hsPDA who fail two courses of medical treatment, are contraindicated for therapy, or persist on full ventilator support (42). It is performed through an open thoracic method by tying off the vessel or using a metal clip. Another technique known as coil occlusion is reserved for neonatal weighing above 5 kg. Many adverse effects are associated with PDA closure, such as postoperative hypotension, vocal cord paralysis, diaphragm paralysis, BPD, and diminished neurodevelopmentation (43).

Cyclooxygenase and Peroxidase inhibitors

Indomethacin

Indomethacin is an NSAID with analgesic, antipyretic and anti-inflammatory properties. It was first discovered in 1963 and was first accepted by the FDA in 1965. In clinical trials, indomethacin is widely investigated as one of the most potent NSAIDs to inhibit PG synthesis. The enzyme that NSAID inhibits is the COX enzyme, which exists in two isoforms known as COX-1 and COX-2. COX-1 is mainly accountable for typical physiological roles through the synthesis of PG for the maintenance of a stable gastrointestinal tract, platelet function, renal function, and other physiological functions. In comparison, COX-2 is responsible for the inflammatory response synthesis of PG (45).

As evident from its chemical structure presented in Figure 1.5, indomethacin is an acetic acid derivative that hinders the conversion of arachidonic acid into PG G_2 by inhibiting the enzymatic activity of the COX enzyme (46). The visual

representation of this mechanism is presented in Figure 1.6 (47). Reduced PG levels in the vascular tissue contribute to the constriction of the muscular wall of the DA leading to hypoxia and subsequent local angiogenesis, neointimal tissue development, and apoptosis (48). These pathways contribute to obstruction and fibrosis processes resulting in anatomical closure of the duct.

Indomethacin has been used for PDA treatment in premature infants since 1976 (46). It was the gold standard for PDA closure for over 40 years with a 70% closure rate. The options for indomethacin treatment based on time of administration are prophylaxis (in the first 24 hours after birth), early symptomatic (within the first three days after birth), and late symptomatic (within 7-10 days after birth) (49). The use of prophylactic treatment was beneficial as it substantially reduces severe IVH, pulmonary hemorrhage, hsPDA, and surgical ligation. However, prophylactic therapy went out of favor due to the lack of improvement in the incidence of chronic lung disease and neurodevelopmental changes at 18 months of corrected age and the unnecessary treatment for a large number of infants who will have spontaneous PDA closure (50). Indomethacin is given intravenously (IV); enteral and rectal routes are not recommended due to increased risk of bleeding in the gastrointestinal tract of neonates. One of the significant side effects of indomethacin is the reduction in mesenteric, cortical, and renal perfusion, which can be effectively reduced with a 36-hour continuous infusion (51). This, in part, is due to the favorable effect of indomethacin on COX-1 instead of COX-2 enzyme (52, 53).

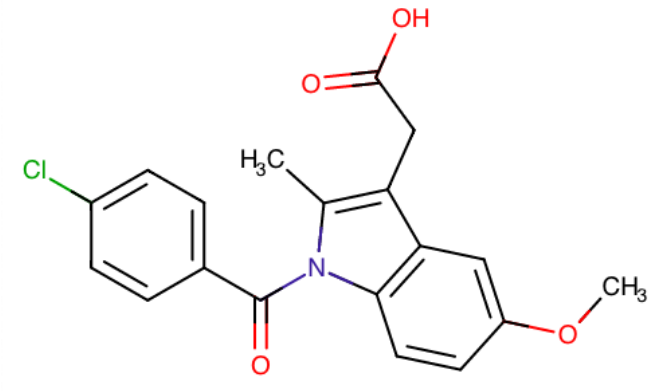

Figure 1.5. Chemical structure of indomethacin

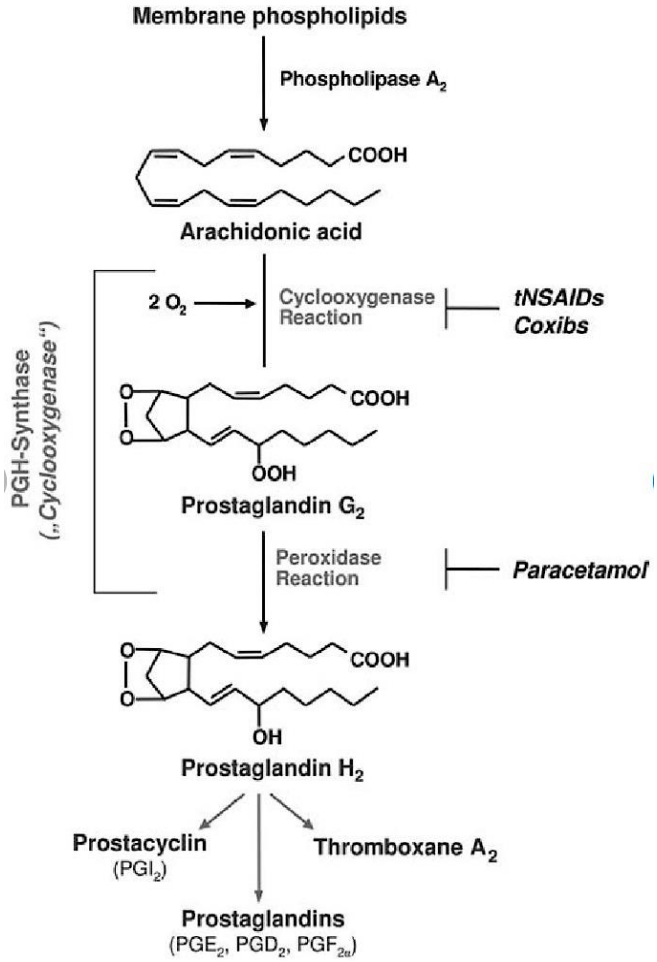

Figure 1.6. Mechanism of action of cyclo-oxygenase inhibitor and paracetamol

Ibuprofen

Ibuprofen, an NSAID, is considered the first propionic acid-based derivative, as presented in Figure 1.7. In 1960, it was developed as a safer alternative to aspirin and was patented in 1961. It was first launched in 1969 and 1974 in the United Kingdom (UK) and the United States of America (USA) for rheumatoid arthritis. Ibuprofen was the first accessible over-the-counter NSAID (54). Only in the mid-1990s it was used in infants for PDA closure. It is also a non-selective COX-inhibitor and, thus, hinders the enzymatic activity of COX-1 and COX-2 with a similar mechanism to indomethacin (Figure 1.5). Although ibuprofen is as efficacious as indomethacin for PDA closure, the lower vasoconstriction leads to a decreased microcirculation effect and less deterioration of intestinal and renal function as a result (53, 55). Ibuprofen is commonly given as an IV preparation in developed countries. However, in many developing countries, IV preparation is costly, with many using the oral form for PDA closure. A recent systematic review reported that the oral form is as effective as the IV form (56).

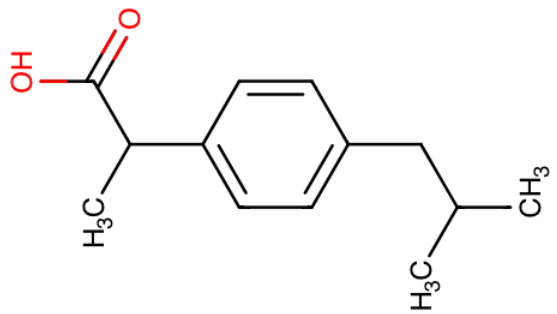

Figure 1.7. Chemical structure of ibuprofen

Paracetamol

Acetaminophen (paracetamol) is the most widely used analgesic globally and is recommended by the World Health Organization (WHO) as the first-line pain therapy, illustrated in Figure 1.8. The FDA originally licensed the drug in 1951, and it is available in several types, including syrup, standard tablets, effervescent tablets, infusion, suppository, and other forms (57). More recently, oral or IV paracetamol administration has grasped interest in PDA treatment; the first case study on this issue was published in 2011 by Hammerman et al. (58). As an alternative therapy, paracetamol is promising for the closure of PDA. This medication has successively been tested in several studies as safe and successful relative to conventional NSAIDs, with fewer side effects for PDA closure (59, 60). Acetaminophen works by blocking the peroxidase site inhibiting the reaction of PG G_2, as presented in Figure 1.6. The peroxidase portion of prostaglandin synthase tends to be inhibited, even under conditions where COX inhibition is less successful as the peroxidase is activated at 10 times lower concentrations than cyclooxygenase. Other advantages are its wide accessibility, low costs, and low risk of premature hepatotoxicity attributed to an immature cytochrome P450 enzyme mechanism (61). With both oral and IV routes of delivery, paracetamol has been shown to be effective. However, as the oral route is hyperosmolar, this should be used with caution in neonates on 'no enteric' or low volume feeding (62). Paracetamol is currently utilized as a treatment option in neonates who are contraindicated to indomethacin and ibuprofen (42).

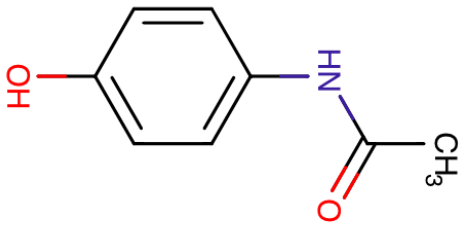

Figure 1.8. Chemical structure of acetaminophen

Pharmacotherapy of PDA in Qatar

In Qatar, the HMC PDA committee recommends ibuprofen IV as the first-line therapy for the management of PDA. The standard dosing regimen of ibuprofen for PDA closure is an initial dose of 10mg/kg IV followed by two additional doses of 5 mg/kg IV at 24-hour intervals. Another course of treatment can be administered in case of failure to close. If the patient does not respond to two courses of ibuprofen, a third course is given with indomethacin if not contraindicated. The standard dosing regimen of indomethacin for PDA closure is an initial dose of 0.2 mg/kg IV followed by an additional two doses of 0.1-0.2 mg/kg IV 12 hours apart (63).

Economic Burden of PDA

The management of neonatal PDA is relatively costly, as it is often inclusive of resource-intensive comorbidities such as RDS. At a time when the emphasis is on containing increasing health expenditures, the national estimates of costs to healthcare institutions in the USA, as an example, reported a total of $176,739 and $99,733 for surgical and non-surgical ligation of PDA, respectively, in extremely immature infants. The USA Healthcare Cost and Utilization Project (HCUP) reveal that the cost of PDA therapy can be as low as $49,457 for neonates who do not undergo surgery and as high as $176,739 for infants who do so. This indicates that ligation-related institutional costs will produce more than $77,000 of increased costs relative to the

PDA's non-surgical treatment (64). Based on data from the Inpatient Public Access Database of Maryland Health Services Cost Review Commission (HSCRC), the estimated gross medication charge for PDA is between 3.8% and 6.2% of the average total medical fees (depending on the neonatal weight). The cost of one vial of IV COX inhibitor is $600, where one vial is used per dose, and any excess dose in the vial must be discarded. As three doses are used in PDA treatment, the prescription cost is $1,800 per PDA case (64).

In the Netherlands, as another example, the average cost per patient for usual care is €92,000 for standard treatment. An annual 270 premature neonates with PDA are treated in the Netherlands, with a consequential burden on a budget of Euros 24,800 (66).

In Qatar, a cohort-based retrospective study was carried out to identify the economic value of pharmacological treatment of premature infants with PDA. The total cost for PDA management per patient using ibuprofen was up to Qatari riyal (QAR) 232,303 (67).

Pharmacoeconomics

Pharmacoeconomics is defined as the description and analysis of the costs of drug therapy to the healthcare systems and society by identifying, measuring, and comparing the costs and consequences of pharmaceutical products and services (68). In particular, pharmacoeconomic research is motivated by the fundamental concept that financial resources are scarce and that organizational needs typically exceed the resources available. In line with a recent public perception of rising healthcare prices, there has been an increased interest in assessing the economics of therapeutic benefits of medications. In a healthcare organization, the evaluation of drugs for integration in the drug formulary can be an overwhelming process. It considers many factors

concerning effectiveness, efficacy, safety, availability, cost, quality, clinician and patient acceptability. The practical application of Pharmacoeconomics can streamline the decision-making process. Decision-makers utilize this tool in healthcare organizations to guide the decision-making process by comparatively evaluating health interventions based on their outcomes and costs. As a result, pharmacoeconomic studies help to provide evidence on pivotal options, such as identifying the best therapeutic plan for handling a specific disease state or the drugs to include in the hospital formulary (68, 69).

The outcome of pharmacoeconomic research is a consequence of the intervention/drug therapy. The critical effects of pharmacologic treatment usually assessed by pharmacoeconomic studies are clinical, humanistic, and economical. Clinical outcomes include medication treatment effects that can be both desirable (cure) and undesirable (side effects). In comparison to clinical outcomes, humanistic outcomes involve what is important as a consequence from the patient's point of view. These outcomes tackle issues such as how a patient feels and what the quality of life (QOL) is perceived to be. In comparison, economic outcomes are the costs associated with therapy, including several distinct forms of costs for consideration in the pharmacoeconomic analysis (69).

Types of Costs

The cost of interventions can be primarily categorized into direct, indirect, and intangible costs. Firstly, direct cost is the value of physical resources used as a consequence of the medical condition. Direct costs can be subdivided into (i) direct medical and (ii) direct non-medical costs. Direct medical costs are related to resources that are medical in nature, such as medication and medical procedures. They, as examples, will include procurement costs, costs of preparation, costs of monitoring,

and fees for doctors. Medication administration costs (e.g., IV administration sets) and/or treating an adverse drug reaction are also considered direct medical costs. Whereas direct non-medical costs include costs of resources that are not medical in nature but directly related to the medical services, such as transportation to the healthcare facility, travel to receive care, and the assistance offered, including, for example, home care and childcare services. Secondly, indirect costs result from productivity loss, i.e. work days missed as a consequence of the morbidity and mortality of the medical condition/intervention investigated. Although not recognized widely as significant, these costs can substantially affect the overall expenses of therapies and/or diseases. Lastly, intangible costs are costs that can be identified but not quantified and may significantly impact the patient's well-being and QOL. For example, they include pain and suffering due to an illness. It is difficult, therefore, to allocate monetary values to intangible costs (68, 69).

Perspective

The perspective is a significant element to consider in the pharmacoeconomic analysis. The perspective is defined as the point of view from which the research is conducted, where this determines the type of costs to be collected and included in the research analysis (61). As per the decision model developed, these cost data are based on resources consumed in the development of consequences. The most common research perspectives include the following (68, 70, 71):

a) Payer perspective: This covers the type of costs that primarily relate to third-party plans (insurance schemes) or patients, or a combination of both. From a patient-only perspective, the patients' out-of-pocket payments are calculated, including travel and transportation as examples.

b) Hospital perspective: This accounts for the cost of hospital services that are direct medical in nature, such as medications, medical tests, and hospital stay.

c) Societal perspective: This is the most comprehensive perspective as it takes into account all expenses, including direct medical and non-medical, indirect and intangible costs.

Types of Pharmacoeconomic Evaluations

For the economic evaluations of health interventions, there are four specific types used (Table 1.4). In all methods of evaluations, the cost is measured in monetary units and always handled and measured similarly. However, how the health effect is handled and measured varies between the different types of studies.

Table 1.4. Four Types of Economic Evaluations

Evaluation method	**Cost measurement unit**	**Outcome measurement unit**
Cost-minimization analysis (CMA)	Monetary units	Assumed to be equivalent
Cost-effectiveness analysis (CEA)	Monetary units	Natural units (Life years)
Cost-benefit analysis (CBA)	Monetary units	Monetary units
Cost-utility analysis (CUA)	Monetary units	Quality-adjusted life years

CMA is the most uncomplicated analysis to conduct where the outcome of two or more health interventions is assumed to be equivalent, with the only cost being different between the interventions. Because it is unlikely for most competitive interventions in practice to have equivalent outcomes, the use of the CMA study design is constrained in practice and is limited in the literature. Even if two interventions can have an equivalent performance for the same indication of use, their side effects may not be similar (72).

CEA is the most frequent economic assessment tool in the health sector. It evaluates two or more health-related interventions based on the same natural (physical) unit of the outcome, but at different levels of performance, such as when

comparing two different drugs for blood pressure control. CEA's main advantage is that outcomes are easily quantified, whereby healthcare professionals are very familiar with the natural units, and they have them readily available. A drawback of CEA is that it only analyzes the clinical dimension of an outcome of an intervention. It cannot consider the QOL outcomes as an example. Another downside of CEA is that two interventions can only be compared against a single outcome measure unit at a time. Comparing two interventions, taking into consideration multiple indications for the interventions, requires multi-CEAs performed. The trade-off between cost and effect in a CEA is mostly presented via the incremental cost-effectiveness ratio (ICER), reflecting the value of money paid with one intervention over another for an additional natural unit outcome. The decremental cost-effectiveness ratio (DCER) can also be calculated, reflecting money saved against a lost unit of outcome. The ICER is computed only when there is no dominancy between the comparators, i.e., one comparator has a higher effect and lower cost than the other comparator. Table 1.5 is a cost-effectiveness grid that demonstrates the different potential scenarios of how two interventions can compare to each other based on cost and effectiveness. In scenarios B, C, and F and D, G, and H, decisions are straightforward and easy, where there is an apparent dominating intervention over another. In contrast, in scenario A and I, there is an intervention with a lower effect but a lower cost, or a higher effect and a higher cost, than the comparator. Here, decisions are complicated, and a trade-off analysis between cost and effect needs to be investigated, which is where an ICER becomes essential to calculate (68, 73).

Table 1.5. Cost Effectiveness Analysis (CEA)

	Lower cost	Same cost	Higher cost
Lower effect	A (calculate ICER)	B	C
Same effect	D	E	F
Higher effect	G	H	I (calculate ICER)

CBA is a type of analysis that values all benefit and costs measurements into a single unit, a monetary unit. Since money is the most obvious metric, CBA includes a monetary evaluation of all relative resources. The monetary valuation of both costs and benefits has two fundamental benefits for decision-makers. First, it explicitly enables determining whether the benefits of an intervention outweigh the costs of its implementation. Second, multiple interventions, regardless of how different their clinical outcome measures are, can be compared. With CBA, the main drawback is the challenge of assigning a monetary value to some health-related or non-monetary outcomes, such as patient satisfaction, which is easily subjective (69).

CUA is similar in methods to CEA as it compares alternative interventions by assessing the trade-off between differences in costs and effects. However, rather than evaluating costs against natural or therapeutic units, CUA tests costs against outcomes in terms of health-related utility, i.e., happiness or well-being. In this analysis, the quality and quantity of life are combined in a single index, the quality-adjusted life years (QALY). QALY incorporates the life years and the health related QOL (HRQOL). A numerical estimate of QOL related to a particular disease state or treatment is known as a utility. The utility is a value between 0 and 1, with 0 representing the death state and 1 representing the healthy state. The advantage of CUA is that it incorporates multiple dimensions of outcomes; clinical and humanistic. Also, like with the CBA, an advantage is that different interventions do not

necessarily have to have similar types of outcome measures to be compared. Regardless of the indication or outcome measure, once various interventions are measure in QALY, they are comparable. The analysis of CUA estimates the cost of an intervention over another per additional unit of QALY. A major drawback of CUA is the highly subjective tools available to quantify the value of utility for the QALY calculations (74).

Decision Analyses

Decision analysis is an analytical method that facilitates decision-making based on a comprehensive comparison among available interventions by following up and evaluating the relative outcomes and consequences of each intervention. In this, the probability, the resource utilization, and the cost value of each outcome and consequence of interest are calculated with any intervention. To aid in the visualization of the decision analysis, a decision tree model is constructed, as illustrated in Figure 1.9 as an example. The decision-analytic model follows the different interventions and their clinical and economic consequences over a predefined duration. Decision-analytic modeling has been relatively and increasingly simplified recently with the availability of several specialized software, with the @Risk® (www.palisade.com) and Treeage® (www.treeage.com/) as the most popular examples. The emphasis of decision analysis in CEA has recently expanded from contrasting decision alternatives in terms of their impact on life and death, to the amount for the extension of life and on measurements of QOL (68, 73).

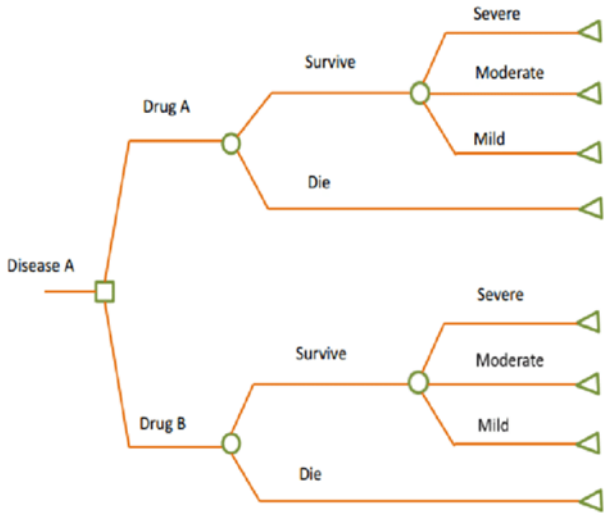

Figure 1.9. Decision tree

Sensitivity Analysis

The sensitivity analysis is to investigate changes in the results of pharmacoeconomic analysis against input uncertainty. Based on the sources of model inputs, which can be the literature of an expert opinion as examples, the value of inputs can be associated with a level of uncertainty. The process involves re-running the analysis several times, whereby in each run, a replacement of the value of an uncertain input by a value from an assigned range of value uncertainty, which can be a 95% confidence interval (CI) for an instant, takes place. Variations in the study's base-case conclusion are then examined, including correlating the distribution of input variability with the distribution of outcome variability. The sensitivity analysis can be classified into (69, 74):

a) One-way deterministic sensitivity analysis involves modifying the value of one model input, leaving the remaining inputs as they are at the base-case.
b) Multivariate probabilistic sensitivity analysis involves the simultaneous modification of two or more model inputs in an analysis. This enables a

reflection of real-life simultaneous ambiguity as it summarizes the aggregate effect of uncertainty in multiple inputs simultaneously.

c) The scenario sensitivity analysis involves a base-case scenario, for instance, on a methodological approach or assumption replaced by a new scenario before the model is re-run. It is worth noting that here it is not the value of the input variable that is changed rather the nature of the revisited input.

Qatar's Profile

Qatar is a peninsula in the Middle East located among the western bank of the Arabian Gulf. It is around 100 km across and stretches 200 km into the gulf. The current recorded population is 2,911,107, equivalent to 0.04% of the world population (75). Qatar is well recognized for its cultural diversity due to the increasing influx of expatriates in the country. In 2021, the Qatari citizens only account for less than 15% of the total population (76).

In Qatar, the gross domestic product (i) added to $155.57 billion (2021) (77). Under the Ministry of Public Health, the public health services in Qatar are provided by two non-profit government-owned organizations: HMC and Primary Healthcare Corporation (PHCC). In addition, the private sector plays a role in delivering healthcare services. While private healthcare services are becoming more prominent, the HMC and PHCC coverage accounts for over 90% of the country's population. PHCC covers the primary care services, while inpatient care is covered by HMC (78).

In 1957, Al-Rumailah Hospital was opened as the first government hospital in Qatar, which then became a member of the HMC when it was established in 1979. Since then, Qatar has seen unprecedented growth in the health sector. HMC currently has 12 hospitals in its portfolio – nine specialized facilities and three community hospitals – with a total of around 2,500 beds. For the PHCC, this includes 27 national

health centers distributed across the country. The private sector accounts for six private hospitals and more than 200 private polyclinics in the country, and a host of clinics, labs, pharmacies, and medical centers. All Qatari nationals are provided with unrestricted free services in all government-based sectors. Whereas for non-Qatari citizens, most of the essential healthcare needs are entirely provided by the government insurance scheme (79).

Some HMC hospitals provide NICU services for critical and non-critical infants born prematurely. The NICU of Women's Wellness and Research Center (WWRC) is the country's largest and most comprehensive facility. It is a tertiary NICU located in the capital city, Doha, with over 100 cots (80). Other hospitals that also offer NICU services include Al-Wakrah Hospital (AWH, with 20 cots offering level II unit of care) (78) and Al-Khor Hospital with a 10 cot capacity (82). In the private sector, Sidra Medicine delivers world-class NICU services for critically ill neonates who require the highest level of care (83).

CHAPTER 2: LITERATURE REVIEW, RATIONALE, OBJECTIVES

Literature Review

Over the last four decades, PDA management has progressed from demanding prophylactic closure using pharmacotherapy or surgical operation to more conservative-based approach (59, 84). Conservative management approaches vary from selective pharmacotherapy (based on echocardiographic findings) to no PDA treatment, apart from supportive measures such as ventilator and fluid restriction (59).

Since targeted PDA management has become the preferential approach, pharmacotherapy selection has become more relevant (85). The first-line therapy for hsPDA is the NSAIDs, either indomethacin or ibuprofen. For patients who do not respond to NSAIDs or pharmacologic treatment is not suitable, surgical ligation is the last resort (86, 87, 88). Surgical management of PDA can have severe complications that may involve reversible complications, including pneumothorax, poisoning, hemorrhage, and permanent complications, including diaphragmatic and vocal cord paralysis.

Traditionally, indomethacin has been the preferred medication in the treatment of hsPDA. Yet, despite its proven effectiveness, its use has been associated with complications related to reduced cortical, renal, and mesenteric perfusion (89, 90). Ibuprofen has demonstrated similar effectiveness value by up to 80%; however, it was associated with a lower incidence of adverse events (AEs) such as NEC and acute renal insufficiency relative to indomethacin (89, 90). Oral acetaminophen has lately emerged as a new therapeutic choice as an alternative to ibuprofen, although it is still considered an off-label medication for PDA treatment. It was first reported in 2011 when Hammerman et al. documented a case series of paracetamol use as hsPDA treatment in five neonates that had either failed or had contraindication of ibuprofen

therapy (58). The rate of ductus closure was 100%, with no AEs recorded. Other case series and research studies testing this novel therapeutic choice were reported in the subsequent years (91-95).

A variety of systematic reviews of RCTs and recently published RCTs have documented head-to-head analyses of paracetamol versus COX inhibitors:

Jasani et al. (96), in 2018, performed a pooled analysis of seven RCTs comparing paracetamol to any COX inhibitor, there were no differences in PDA closure rates between 861 neonates following the first course of treatment (relative risk (RR) 0.90; 0.72–1.13) and lower gastrointestinal hemorrhage (RR 0.51; 0.28–0.91) associated with paracetamol therapy. There were no variations in the rates of ROP, BDP, NEC, IVH, pulmonary hemorrhage, mortality, or surgical ligation.

Huang et al. (97), in 2018, conducted a meta-analysis (MA) of five RCTs involving 677 infants treated with paracetamol or ibuprofen. The primary and overall PDA closure rates between paracetamol and ibuprofen were similar, RR 1.03, P=0.56 and RR 1.02, P=0.62, respectively. No differences were observed in the occurrence of PDA complications of NEC (RR 0.86, P=0.70), BPD (RR 0.69, P=0.16), ROP (RR 0.58, P=0.15), IVH (RR 0.84, P=0.55) and death (RR 1.45, P=0.45). However, paracetamol demonstrated a decreased incidence of kidney dysfunction (RR 0.20, P=0.07) and a substantially diminished risk of gastrointestinal bleeding (GIB) (RR 0.28, P=0.009).

The Cochrane Systematic Review conducted by Ohlsson et al. (98) in 2020 involved eight reports that recorded data obtained from 916 neonates. Studies that have attained at least moderate GRADE quality evidence have shown that paracetamol is as effective as ibuprofen. In contrast, a group of low-quality evidence studies has indicated that paracetamol is more effective than placebo and is as

effective as indomethacin in PDA treatment. Paracetamol was reported to be a viable alternative to indomethacin or ibuprofen for PDA closure, possibly with less AEs.

Soni et al. (99), in 2020, conducted an RCT comparing the efficacy and safety between all three-treatment options, oral indomethacin, oral ibuprofen, and IV paracetamol, for the closure of PDA in preterm neonates. The study showed no significant difference in PDA closure rate among all treatment options with 68%, 77%, and 71% in the indomethacin, ibuprofen, and paracetamol groups, respectively (P=0.716). No NEC and GIB occurred in neonates after treatment with paracetamol; however, NEC and GIB cases were observed in the indomethacin and ibuprofen group.

In 2020, Kumar et al. (100) conducted a non-inferior RCT trial on 161 infants (average GA of 28 weeks) to compare oral paracetamol with oral ibuprofen. The study's primary outcome was the closure rate of hsPDA within 24 hours from the last dose of the medication. The outcomes per-protocol analysis indicated similar PDA closure rates for oral paracetamol versus oral ibuprofen (95.4% versus 94%, RR 1.01, 95% CI (0.94-1.1)). More infants in the oral ibuprofen group had oliguria and major IVH while definite NEC was observed in the oral paracetamol group; however, this was not statistically significant.

Rationale

In HMC in Qatar, the pharmacy and therapeutics (P&T) committee regulates drug selection. Given that medication represents one-fifth of HMC expenditure, there is a need to ensure the most appropriate drug is being utilized (101). The process of selecting formulary drugs according to efficacy, safety, and cost-effectiveness will ensure the optimization of quality and safety of patient care and resultant health outcomes. However, PDA's optimal management is highly controversial and remains

unclear as there are no universal guidelines or consensus regarding the most appropriate pharmacological treatment and route of administration. This uncertainty in selection is further emphasized when considering that relative variability in the effectiveness and safety performance of therapies is consequentially associated with a relative economic impact.

Currently, the selection of pharmacological treatment for PDA is dependent on individual institutions. In HMC in Qatar, the preferred first-line treatment is IV ibuprofen, which is not based on any local comparative evidence, even though the IV indomethacin is also available in the HMC drug formulary for PDA closure. Traditionally, treatments have been given via the IV route, but the oral route is now increasingly considered. Oral ibuprofen, and now oral paracetamol, have become popular options in many NICUs. In Qatar, there is an increasing trend of using oral ibuprofen as well as oral paracetamol. This, however, is all arbitrary, based on personal preference and again, not based on any local evidence. One element in favor of the decision is the lower cost of oral administration than the IV (102). Indeed, the lower acquisition cost of oral ibuprofen has not only been a driver for use in low-income countries but is reported to be so in 29% of NICUs in high-income European countries as well, and without proper evaluations of overall costs (103). When it comes to paracetamol use for PDA, whether oral or IV, several advantages for a first-line use can be proposed. First, the cost of oral or IV paracetamol acquisition is very low compared to IV indomethacin and IV ibuprofen. Second, paracetamol is associated with reduced GIB and renal insufficiency, which could further add to the economic advantage of paracetamol.

Therefore, in order to choose the most optimal treatment, there is a need for Qatar-based research that aims to analyze the cost of ibuprofen compared to

indomethacin and paracetamol in PDA at HMC in Qatar. Assessing the impact of resource consumption is most important for better understanding of the effect of different pharmacological agents on hospital budgets for decision-makers and practitioners to consider beyond the acquisition costs, including when revising HMC's protocols and practices.

Internationally, there are no economic evaluations on how different formulations compare for the treatment of PDA. The only such study is a local Qatar study, by Abushanab et al. (67), to better differentiate the oral versus IV formulations of ibuprofen, which was a cohort-based cost-effectiveness study on 124 neonates from the primary NICUs in HMC. Premature neonates with hsPDA were distributed into one of two groups; oral ibuprofen and IV ibuprofen. The oral ibuprofen achieved a closure success of 64% in comparison to 52% with the IV ibuprofen. Taking cost into consideration, the oral ibuprofen was between dominant and cost-effective against IV ibuprofen for PDA treatment. Regarding AEs, a case of NEC was identified in the oral ibuprofen study group, which resolved without intervention, whereas 4 cases of AEs occurred in the IV group, including two intestinal perforations, self-resolved NEC, and thrombocytopenia.

Consequently, a follow-up study to Abushanab et al. (67) is required for evaluating the cost-effectiveness of ibuprofen versus each of indomethacin and, especially, paracetamol, which was never evaluated economically for the management of PDA. For the purpose of economic evaluations among ibuprofen, indomethacin, and paracetamol in HMC, a local cohort design is not feasible at this stage. This is because the indomethacin and paracetamol options are currently only randomly used in the Qatari NICU and, hence, there are no sufficient neonatal records to utilize as data sources. Hence, a simulated cohort-based, comparative economic model that is

populated with literature data on the performance of the study drugs is relevant and appropriate. Here, our preliminary literature search suggested that there are numerous MAs published for the purpose of combining different head-to-head studies for the use of ibuprofen versus indomethacin, and ibuprofen versus paracetamol, for PDA in neonates. The MAs, however, are associated with multiple objectives and contrasting results and with varying levels of methods quality and risk of bias. This, therefore, potentially limits how easily accessible the best evidence is. Within this context, the systematic review of MAs is a recent study design for the purpose of addressing the growing problem of information overload, enabling an approach to filter large volumes of evidence. This will not only help identify the best of sources of evidence for our proposed economic evaluation of the therapies in PDA but will also enhance the access of the international audience to the published evidence and, therefore, better inform healthcare decision-making.

Study Objectives

Phase One: Use of ibuprofen for the closure of PDA in preterm infants. A systematic review of meta-analysis

The objective of this phase was to conduct a summative assessment of all the published MAs comparing ibuprofen to other treatment such as indomethacin and paracetamol for the treatment of PDA, including the quality assessment and risk of bias. This was carried out to enable the filtration of large volume of evidence to enhance access to targeted evidence.

(To note, Phase One of this study has been accepted for publication as follows: *Al-Shaibi S, Abushanab D, Alhersh E, Kaddoura R, Pallivalappila A, Al-Badriyeh D. Use of ibuprofen for the closure of patent ductus arteriosus in preterm infants: a*

systematic review of meta-analyses. Journal of Comparative Effectiveness Research. 2021;10(7):549-568.)

Phase Two: Cost-effectiveness analysis of ibuprofen versus indomethacin or paracetamol (acetaminophen) for the treatment of PDA in preterm neonates

The second phase of this thesis's objective is to construct a comprehensive simulation-based economic decision-analytic model to evaluate the cost-effectiveness among different formulations of ibuprofen against each of indomethacin and paracetamol as first-line treatment options for PDA closure in preterm infants. This CEA is explored from the perspective of the intensive care setting of HMC in the State of Qatar.

CHAPTER 3: MATERIAL AND METHODS

As stated in the thesis objectives in Chapter 2, there are two phases in this research. Here, the methods for each of the two phases are described separately.

Phase One: Use of Ibuprofen for the Closure of PDA in Preterm Infants. A Systematic Review of Meta-analysis

(This phase of the thesis has been derived from the following publication: Al-Shaibi S, Abushanab D, Alhersh E, Kaddoura R, Pallivalappila A, Al-Badriyeh D. Use of ibuprofen for the closure of patent ductus arteriosus in preterm infants: a systematic review of meta-analyses. Journal of Comparative Effectiveness Research. 2021;10(7):549-568.)

This is a systematic review that follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as relevant in Appendix A. The PROSPERO registration number for this systematic review is CRD42020165457.

Included Studies

MAs of RCTs or quasi-experimental design and observational studies, investigating the use of ibuprofen, including versus paracetamol or indomethacin, for the treatment of PDA in preterm infants. Excluded publications included expert opinions, narrative and qualitative reviews, previous versions of current/updated MAs, and ibuprofen's use for prevention against PDA. Also excluded are the MAs of studies that were all included in more recent MAs that are included in our analysis. However, such older MAs were included in the current analysis if reported pairwise comparisons between interventions that were not included in the more recent MAs.

Participants

Preterm infants (≤37 weeks) with hsPDA. There were no inclusion or exclusion criteria on birth weight or postnatal age.

Interventions

Ibuprofen versus indomethacin or paracetamol, via any formulation and dosing regimen, or comparing different formulations or doses of ibuprofen, for the treatment of PDA.

Outcome Measures

Outcomes of interest were efficacy and safety outcomes of ibuprofen. Successful PDA closure was the outcome of interest, and there were no inclusion or exclusion criteria on the reporting of other outcomes. The analysis in this review only included outcomes reported in two or more MA/network MA (NMA). As reported in included studies, the effect measure of ibuprofen could be a RR, odds ratio (OR), or mean difference (MD). These were provided at 95% CI. For NMAs, the SUCRA (surface under the cumulative ranking curve) measures could be included, presented by a mean SUCRA score and a median ranking for the treatment modality.

Search Strategy and Selection of MAs

We searched Embase, PubMed, and the Cochrane Database of Systematic Reviews (CDSR). Search terms used were based on variations of the key terms' ibuprofen' and 'patent ductus arteriosus' in literature, from inception to June 2020. Detailed search strategies are in Appendix B. Google Scholar, and references of the included studies were manually searched for additional relevant articles in the grey literature over the same search duration. An English language restriction was imposed on the search.

Two reviewers independently screened the identified studies based on the above criteria, including duplicate removal, first by title and abstract for an initial eligibility assessment, before a final full-text screening. Any disagreement was resolved by consensus and referral to a third reviewer. With a similar process, two reviewers independently extracted the main study characteristics and the outcomes of interest.

Quality of Methods Assessment

As generally performed in the literature (104), the quality of methods and risk of bias are evaluated for included MAs to enable the interpretation of conclusions identified from the MAs. Two reviewers independently assessed MAs' methodological quality based on AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews-2, https://amstar.ca/Amstar_Checklist.php) (105). No identified tool has been proposed to especially evaluate the methodological quality of NMAs. Because of its good validity, reliability, and responsibility, AMSTAR-2 is currently the most commonly used tool for the assessment of methods quality in MAs and, in the current study, consistent with relevant similar studies in the literature (106), will also be used to assess the quality in NMAs. The quality of methods was rated as high, moderate, low, and critically low. Disagreements were resolved by consensus and referral to a third reviewer.

Risk of Bias Assessment

The ROBIS (Risk of Bias in Systematic Reviews) tool (107) is most proposed for assessing the risk of bias in MAs, including NMAs. Two reviewers independently evaluated the risk of bias in the studies. The risk of bias was rated 'high risk of bias', 'unclear risk of bias', or 'low risk of bias'. Disagreements were resolved by consensus and referral to a third reviewer.

Phase Two: Cost-effectiveness of Ibuprofen versus Indomethacin or Paracetamol for the Treatment of PDA in Preterm Neonates

Phase two of this thesis is a CEA model of oral and IV ibuprofen treatment versus each of IV indomethacin and oral paracetamol in premature neonates with PDA from the perspective of HMC in Qatar.

The Structure of the Model

Two decision-analytic simulation models were constructed to reflect the use of different treatment alternatives and their possible consequences of interest as first-line therapies for PDA closure in premature infants. The relative costs and outcomes of each treatment pathway in the model are rigorously compared. One decision-analytic model was constructed to compare (i) oral ibuprofen versus IV indomethacin and (ii) IV ibuprofen versus IV indomethacin. Figure 3.1 is a schematic representation of the model tree structure showing the follow up of oral ibuprofen, IV ibuprofen, versus IV indomethacin. The second decision-analytic model compared (i) oral ibuprofen versus oral paracetamol and (ii) IV ibuprofen versus oral paracetamol. With an identical structure, Figure 3.2 is a schematic representation of the model with the follow-up pathways using oral ibuprofen, IV ibuprofen, and IV paracetamol. As seen in Figure 3.1 and Figure 3.2, the decision model had six possible pathway outcomes of interest. Directly comparing oral to IV ibuprofen, or indomethacin to paracetamol, for PDA is not of interest in the current research.

With all therapies (indomethacin, ibuprofen, or paracetamol), neonates received the medication for one course of treatment. Comparing ibuprofen to indomethacin (Figure 3.1) constituted (i) oral ibuprofen of 10 mg/kg initially followed by 5 mg/kg given at 24 and 48 hours, (ii) IV ibuprofen of 10 mg/kg initially followed by 5 mg/kg given at 24 and 48 hours, (iii) IV indomethacin of 0.2 mg/kg given at 12

hours' intervals for three doses. For comparing ibuprofen to paracetamol (Figure 3.2), this constituted (i) oral ibuprofen of 10 mg/kg initially followed by 5 mg/kg given at 24 and 48 hours, (ii) IV ibuprofen of 10 mg/kg initially followed by 5 mg/kg given at 24 and 48 hours, (iii) oral paracetamol of 15 mg/kg given at 6 hours' intervals for three doses.

The simulated decision model was based on a simulated cohort of premature neonates of <35 weeks GA (average of 28 weeks) and <1.5 kg weight (average of 1.1 kg) (56, 98). The prematurely born neonates diagnosed using echocardiography to have a hsPDA (>1.5 mm) were qualified for pharmacological treatment of PDA unless contraindicated. Contraindication criteria for the management of hsPDA using pharmacological treatment include major congenital malformations, life-threatening infection (sepsis), urine output <0.5 ml/kg/hr for 8 hours before treatment, serum creatinine >1.8 mg/dl, platelets <50, 000/uL, active NEC stage 2 or 3 (Bells staging criteria), active bleeding or intestinal perforation, IVH grade 3 or 4, liver dysfunction, and severe hyperbilirubinemia.

For each treatment course, neonates were primarily differentiated into a "success" or a "failure" health state. Success is defined as the closure of PDA with or without an AE that does cause premature discontinuation. Closure of PDA is known as the closure within one week of administering the first dose of medication. In contrast, failure is defined as no closure due to no response to the first course of treatment, death or premature discontinuation of therapy due to AEs. No response to the first course is defined as neonates with persistent hsPDA that requires a repeat course or is contraindicated to medications and will require surgery. Death is defined as all-cause death during the initial hospital stay. Premature discontinuation is described as an incomplete course of pharmacological treatment due to AEs, which

included pulmonary hemorrhage, IVH, NEC >1, GIB, intestinal perforation, and oliguria. AE is defined as an undesirable or harmful outcome that develops during or after using a drug (108). In premature infants, an AE can occur in both a success and a failure case. This was distributed in the decision model based on their period of occurrence according to the GA of premature neonates with PDA. The AEs reported were based on the clinical data available in the literature for the evaluation of each pair. The AEs that were reported with success include ROP, PVL, and BPD. In premature infants with a GA of 27 weeks, the mean GA of developing ROP is reported after 30 weeks. Therefore, this is considered a long-term event and is not to occur in the first week of treatment (109). Moreover, as part of the routine screening for infants with GA < 30 weeks, ultrasound screening is performed at 10-14 days and repeated at 36 weeks as there are two phases for the evolution of PVL. The first phase is the early acute phase that could occur after the first week to 10 days, and the late chronic phase that evolves over 4-6 weeks (110). BPD is evaluated in infants who use mechanical ventilators over a long time, where it is diagnosed at 36 weeks of PMA (111). Hence, as the ROP, PVL, and BPD events do not occur over a short-term exposure to PDA (in the first week of treatment), these events were assumed to not contribute to premature discontinuation of medication in the model. On the contrary, the AEs to contribute to the premature discontinuation of treatment were events that could occur over a short time during or after the treatment period; an AE due to medication intake and PDA. These events included pulmonary hemorrhage, IVH, NEC >1, GIB, intestinal perforation, and oliguria. The duration of the model follow-up was based on the duration of hospitalization until discharge.

An HMC-based expert panel of well-qualified professional healthcare providers validated the model structure. The panel included one neonatology

consultant, one specialist and one senior clinical pharmacist, who all have clinical experiences with PDA treatment. Contrasting opinions were discussed among the panel members until consensus.

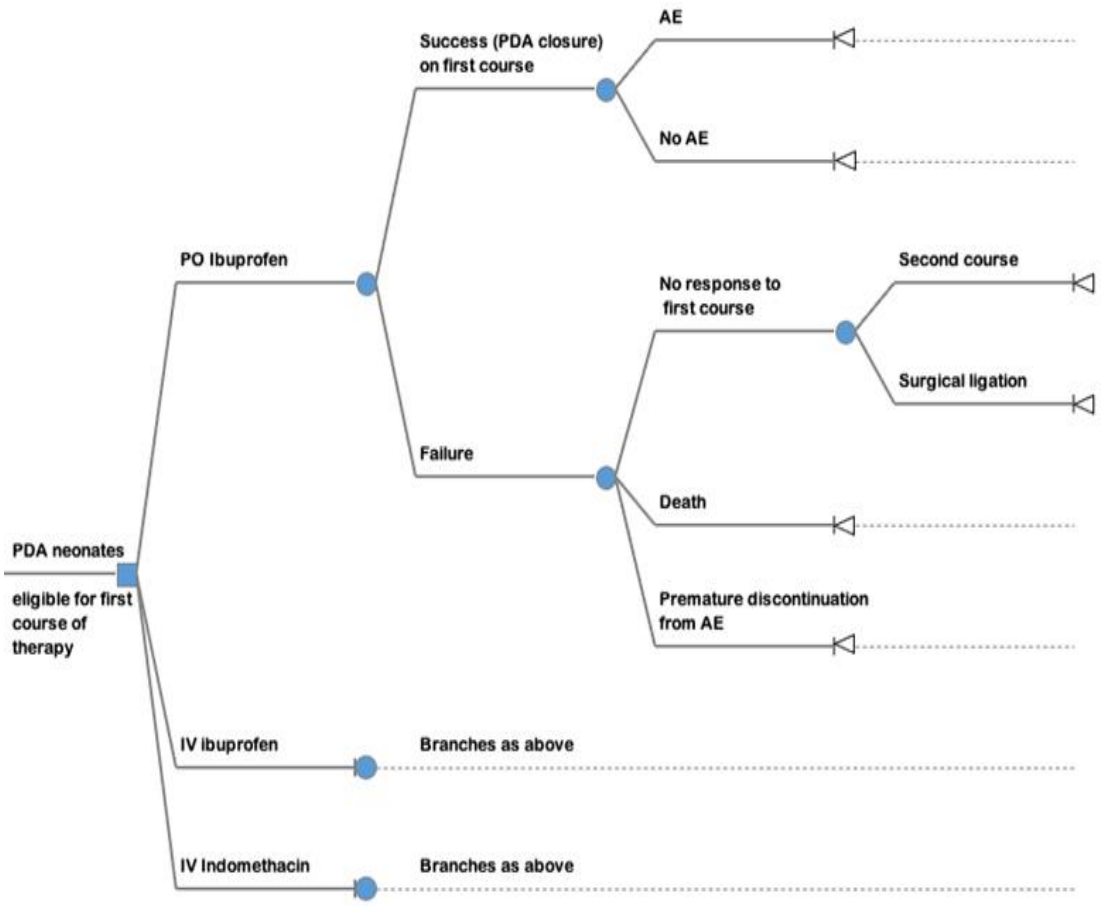

Figure 3.1. Decision-tree based model for patent ductus arteriosus (PDA) therapy of oral/IV ibuprofen versus IV indomethacin

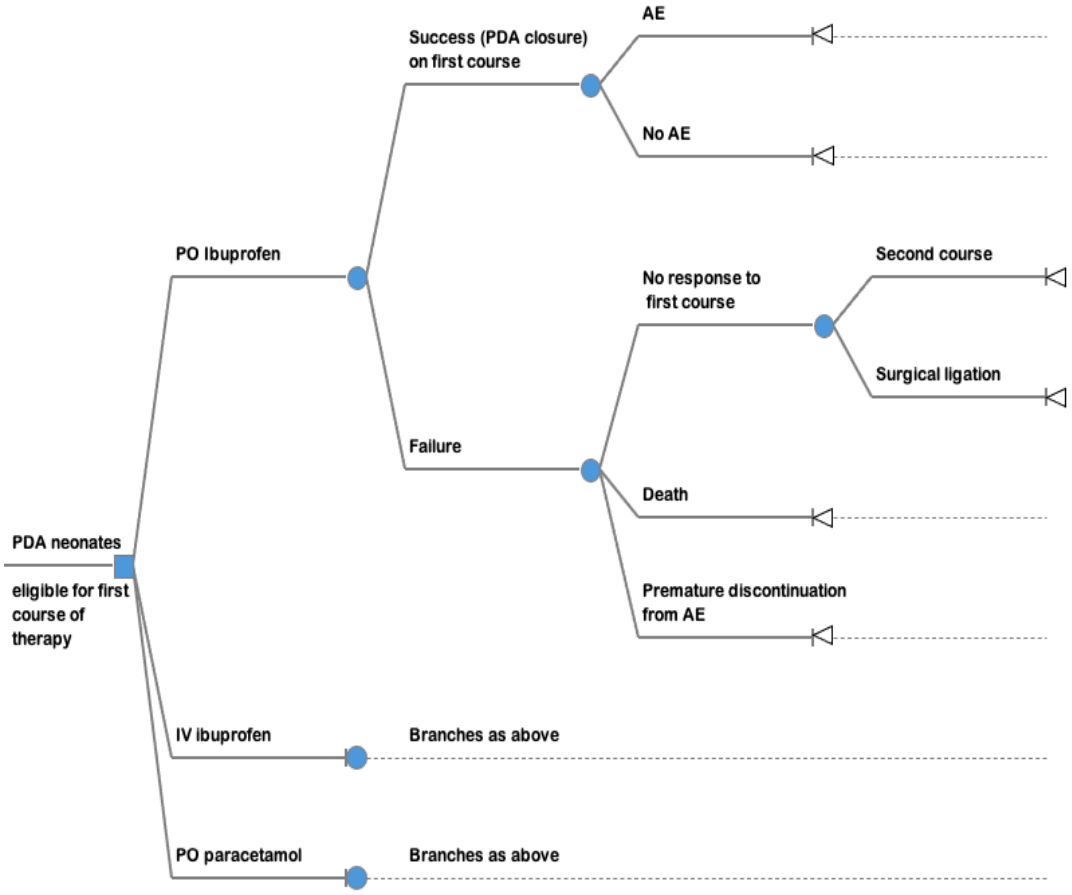

Figure 3.2. Decision-tree based model for patent ductus arteriosus (PDA) therapy of oral/IV ibuprofen versus PO paracetamol

Study Perspective

The decision-analytic model was performed from the HMC perspective. Hence, only the cost of direct medical resources was considered, including medications, hospitalization, diagnosis, treatment, and adverse events management. Other types of costs, including indirect, intangible, and non-medical costs, were neglected.

Model Input

Clinical input data for the oral/IV ibuprofen versus IV indomethacin comparative model were primarily extracted from a MA by Ohlsson et al. (56). For the oral/IV ibuprofen versus paracetamol model, the clinical inputs were obtained from a second

MA by Ohlsson et al. (98). As per the literature review in **Phase One** of this thesis, these relevant MAs and are of the highest quality in the literature (Phase One of Chapter 3). The MA are Cochrane reviews of RCTs of premature neonates hospitalized for PDA. They are the most recent and inclusive reviews in the literature that provide head-to-head evaluations between IV/oral ibuprofen and indomethacin or paracetamol in neonates with PDA. The ibuprofen versus indomethacin MA included 39 RCTs of 2843 infants (56), and the ibuprofen versus paracetamol MA included 8 RCTs that enrolled 916 preterm infants (98). Clinical data that were not reported in the Ohlsson et al. Cochrane reviews were extracted from another recent NMA by Mitra et al., which analyzed 68 RCTs and observational studies of 4802 infants, including all treatment modalities (59). The study drug regimens in the Cochrane reviews and NMA were identical to the routine clinical practice in HMC Qatar, as already discussed in phase 1 of Chapter 3 above. Outcomes in the Cochrane review and NMA were reported as RR and OR, respectively. Outcome probabilities for the decision model were, therefore, calculated using the RR and OR. RR is defined as the ratio of the probability of the event in the intervention group (P_1) to the probability of the same event in the comparator group (P_2). Therefore, P_1 is equal to RR x $P_{0,}$ where RR and P_0 are obtained from the Cochrane review. In the NMA, RR was derived from the OR using the equation: RR= OR/ (1- P_1+ (P_1 x OR)), before the outcome probability was then calculated (112). The probability of all outcomes of events obtained from the studies is presented in Appendix D. This was then used to calculate each pathway's probability based on the decision tree model. To account for underlying uncertainties in the input data of the model obtained from the literature, the base-case of the simulation model was based on multivariate uncertainty analysis, using Monte Carlo simulation through @Risk-7.6 (Palisade Corporation, NY, US).

Monte Carlo is a computerized mathematical technique that permits a simulated cohort of patients based on numerous test runs of the model analysis. For each re-run of the model, the base-case value of the uncertain input variable is randomly replaced by a new input value chosen from within a predefined uncertainty ranges assigned to the model input. At the base-case of our model, all the outcome probabilities were simultaneously varied based on the 95% CI ranges. The probabilities of each of the model's health states are presented in Table 3.1 and Table 3.2 for the ibuprofen versus indomethacin, and ibuprofen versus paracetamol models, respectively. The model simulation was run with 5,000 iterations, and a uniform type of distribution for the selection of random inputs within uncertainty ranges was utilized to overestimate the uncertainty.

Cost Calculation

Cost calculations were based on the financial year 2020/21 and were represented in QAR. This research did not include discounting of costs, given the short timeframe of the analysis. As explained earlier, only direct medical costs were taken into account, assuming that patients have completed the full course of therapy unless the medication was discontinued due to AEs. For the analysis, information on the cost of events was available. The wholesale prices of medications were acquired through the drug supply department of HMC. Clinical event costs were based on the finance department of HMC, which were available as per resource category, calculated based on a micro-costing approach of involved direct medical resources. The medical resource cost categories constituted the costs of hospitalization, monitoring including laboratory tests, diagnostic tests, supportive care, treatment of events including AEs and surgery (excluding diagnostic, monitoring, hospitalization costs) and medications acquisition, as relevant to the events.

The average GA of infants treated for PDA as reported in the MA by Ohlsson et al. (56, 98) is 28 weeks. In HMC, however, PDA requires hospitalization under therapy until 34 weeks of PMA. According to HMC, infants can be discharged from the NICU after 34 weeks of gestation after fulfilling the following criteria (i) the infant can breathe in room air >7 days, (ii) no apneas, (iii) full feeding by sucking, (iv) body temperature is normal in the cot, (v) gaining normal weight of 10-30 g/day, and (vi) mother is ready. Therefore, the neonatal hospital management costs were calculated based on a 7-week duration for success with no event; where there is an event, the duration of handling the event is added on. A course of study drug was given for three days. If this is prematurely discontinued, the duration of the drug is assumed to be reduced by half, two days.

As discussed above, event costs were obtained from HMC, based on the micro-costing of included resources. This was as follows:

a. The cost of a neonate with PDA closure without AEs is the sum cost of medication acquisition over three days, plus the cost of management of PDA when successful as per HMC.
b. The cost of a neonate with PDA closure with an AE is the cost of a neonate with PDA closure (without AEs), plus the AE management cost, as per HMC, for an additional two weeks, except for BPD where three weeks were considered instead.
c. The cost of a neonate without PDA closure and a second course is the sum cost of a neonate with PDA closure (without AEs) plus the cost of managing a successful course of the therapy without AEs for an additional two weeks.
d. The cost of a neonate without PDA closure and surgical ligation is the sum cost of a neonate with PDA closure (without AEs) plus the cost of undergoing

surgical ligation for PDA. The cost of management of an infant undergoing surgical ligation is an additional three weeks.

e. The cost of death is equal to the cost of successful management of PDA treatment without AEs.
f. The cost of premature discontinuation of medication due to AEs is the sum of medication acquisition over two days, plus the cost of AEs management over two additional weeks except for oliguria, where no additional days were considered.

Based on the decision analysis principles of modeling, the overall cost of treatment, incorporating all health states with uncertainties, is the sum of "proportional costs" of all the different health states. The proportional cost of a health state is the 'cost of the health state' multiplied by the 'probability of the health state'. The cumulative cost of a study drug is calculated by adding the proportional costs of all health state pathways for the study drug.

Outcome Measure

The trade-off between the comparative cost and effectiveness outcomes of the study drugs in this model was presented via the ICER per case of overall success, which is the "probability of PDA closure". The ICER is the ratio of the difference in the total cost of two study drugs to the difference in effectiveness (i.e., success) between these two study drugs. When an intervention is dominant over another (higher efficacy and lower cost), where an ICER is not reported, the probabilities of dominance, cost-effectiveness, and not cost-effectiveness were reported. In this study in Qatar, the willingness-to-pay (WTP) threshold (i.e., the cost-effectiveness threshold) against which the ICER is interpreted for whether an intervention is

deemed cost-effective is estimated to be USD 150,000 (QAR 546,150) per case of success.

Sensitivity Analysis

The inputs of the models obtained from the literature are associated with potential uncertainty. In order to evaluate the robustness and increase the generalizability of the study conclusions against this uncertainty, deterministic one-way sensitivity analysis and a probabilistic multivariate sensitivity analysis were conducted.

The one-way sensitivity analyses included evaluating the acquisition cost of medications (-90% and +10% uncertainty) using a uniform type of distribution. Here, a broad –ve uncertainty limit has been used as the medication used in HMC for PDA treatment were brand medications, thus increasing the generalizability of results to practices where cheaper generics are used.

As a follow up on the multivariate uncertainty in outcome probabilities performed at base case, the multivariate sensitivity analysis was conducted to incorporate uncertainty in the cost of management of AEs (±10 uncertainty), using a triangular type of distribution.

As with the base-case, the one-way and multivariate sensitivity analyses were carried out using 5000 iterations using Monte Carlo simulation via @Risk-7.6® (Palisade Corporation, NY, US).

Ethical Approval

Due to the non-human related nature of the data sources in the study models, Qatar University exempted the research from an institutional review board (IRB) review (Appendix C)., and the Medical Research Center (MRC) of HMC did not

require submission and asked that authors to be in direct contact with the finance department of HMC to obtain the cost data.

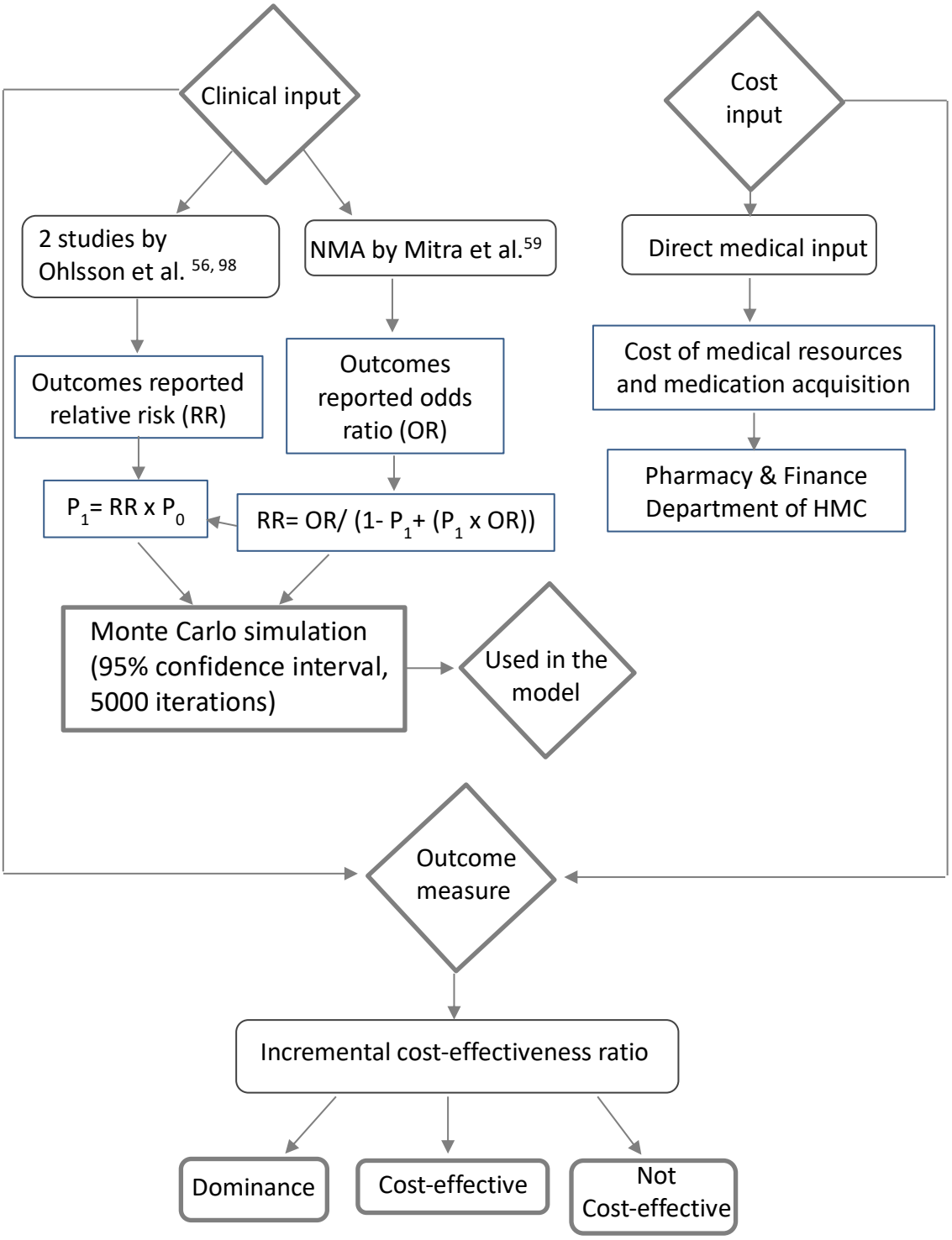

Figure 3.3. Flow chart of the study design showing the method for obtaining clinical input, cost input and the outcome measure. P_1= Probability of event in intervention, P_0= probability of event in the comparator

Table 3.1. Input Variables in the Base-case Multivariate Analysis (Ibuprofen Versus Indomethacin)

Parameter	Oral Ibuprofen (95% CI)	IV Indomethacin (95% CI)	IV Ibuprofen (95% CI)	References
Clinical probabilities				
PDA closure without adverse events[1]	0.538 (0.437, 0.640)	0.351 (0.257, 0.452)	0.341 (0.248, 0.442)	(59)
PDA closure with PVL	0.069 (0.029, 0.139)	0.044 (0.011, 0.099)	0.056 (0.022, 0.126)	(56)
PDA closure with ROP	0.102 (0.049, 0.176)	0.184 (0.110, 0.270)	0.139 (0.079, 0.224)	(56)
PDA closure with BPD	0.194 (0.118, 0.281)	0.177 (0.110, 0.270)	0.190 (0.118, 0.281)	(56)
[2]**No response to first course with second course**	0.011 (0.00, 0.055)	0.039 (0.011, 0.099)	0.064 (0.022, 0.126)	(56, 59)
[2]**No response to first course with surgical ligation**	0.005 (0.002, 0.055)	0.028 (0.006, 0.085)	0.033 (0.006, 0.085)	(56)
[2]**Death**	0.016 (0.002, 0.070)	0.035 (0.006, 0.085)	0.042 (0.011, 0.099)	(56)
[2]**Premature discontinuation with pulmonary hemorrhage**	0.001 (0.00, 0.036)	0.014 (0.000, 0.055)	0.022 (0.002, 0.070)	(56)
[2]**Premature discontinuation with IVH**	0.017 (0.00, 0.055)	0.024 (0.002, 0.070)	0.036 (0.011, 0.099)	(56, 59)
[2]**Premature discontinuation with NEC**	0.007 (0.00, 0.055)	0.019 (0.002, 0.070)	0.018 (0.002, 0.070)	(56, 59)
[2]**Premature discontinuation with GIB**	0.036 (0.011, 0.099)	0.027 (0.006, 0.085)	0.028 (0.006, 0.085)	(56)
[2]**Premature discontinuation with intestinal perforation**	0.003 (0.00, 0.036)	0.026 (0.006, 0.085)	0.020 (0.002, 0.070)	(56)
Premature discontinuation with oliguria	0.001 (0.00, 0.036)	0.034 (0.006, 0.085)	0.012 (0.000, 0.055)	(56)

CI: confidence interval, PVL: periventricular leukomalacia, ROP: retinopathy of prematurity, BPD: bronchopulmonary dysplasia, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, GIB: gastrointestinal bleeding.
[1]Probability of success without adverse event is one minus overall probability of success with adverse event.
[2]The overall probability of all failure events is equal to one minus the overall probability of success.

Table 2.2. Input Variables in the Base-case Multivariate Analysis (Ibuprofen versus Paracetamol)

Parameter	Oral Ibuprofen (95% CI)	Oral Paracetamol (95% CI)	IV Ibuprofen (95% CI)	Reference
Clinical probabilities				
PDA closure without adverse events	0.440 (0.341, 0.543)	0.512 (0.408, 0.611)	0.271 (0.186, 0.368)	(59)
PDA closure with PVL	0.033 (0.006, 0.085)	0.033 (0.006, 0.085)	0.025 (0.002, 0.0704)	(98)
PDA closure with ROP	0.097 (0.049, 0.176)	0.042 (0.011, 0.099)	0.124 (0.064, 0.200)	(98)
PDA closure with BPD	0.056 (0.022, 0.126)	0.046 (0.016, 0.112)	0.051 (0.0164, 0.113)	(59, 98)
No response to first course with second course	0.140 (0.079, 0.224)	0.167 (0.102, 0.258)	0.182 (0.110, 0.270)	(59)
No response to first course with surgical ligation	0.022 (0.002, 0.070)	0.014 (0.000, 0.055)	0.031 (0.006, 0.085)	(98)
Death	0.066 (0.029, 0.139)	0.073 (0.029, 0.139)	0.040 (0.011, 0.099)	(98)
Premature discontinuation with pulmonary hemorrhage	0.031 (0.006, 0.085)	0.033 (0.006, 0.085)	0.112 (0.056, 0.188)	(98)
Premature discontinuation with IVH	0.016 (0.002, 0.070)	0.018 (0.002, 0.070)	0.007 (0.000, 0.055)	(59, 98)
Premature discontinuation with NEC	0.023 (0.002, 0.070)	0.029 (0.006, 0.085)	0.014 (0.000, 0.055)	(59, 98)
Premature discontinuation with GIB	0.035 (0.011, 0.099)	0.014 (0.000, 0.055)	0.006 (0.000, 0.055)	(98)
Premature discontinuation with intestinal perforation	0.002 (0.000, 0.036)	0.000 (0.000, 0.036)	0.003 (0.000, 0.036)	(98)
Premature discontinuation with oliguria	0.038 (0.011, 0.099)	0.020 (0.002, 0.070)	0.135 (0.071, 0.212)	(98)

CI: confidence interval, PVL: periventricular leukomalacia, ROP: retinopathy of prematurity, BPD: bronchopulmonary dysplasia, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, GIB: gastrointestinal bleeding.
[1]Probability of success without adverse event is one minus overall probability of success with adverse event.
[2]The overall probability of all failure events is equal to one minus the overall probability of success.

CHAPTER 4: RESULTS

Phase One: Use of Ibuprofen for the Closure of PDA in Preterm Infants. A Systematic Review of Meta-analysis

(This phase of the thesis has been derived from the following publication: Al-Shaibi S, Abushanab D, Alhersh E, Kaddoura R, Pallivalappila A, Al-Badriyeh D. Use of ibuprofen for the closure of patent ductus arteriosus in preterm infants: a systematic review of meta-analyses. Journal of Comparative Effectiveness Research. 2021;10(7):549-568.)

Study Selection

Out of 1924 studies returning from the literature search, seven studies were included for analysis. A detailed flow diagram of study inclusion is in Figure 4.1. A list of excluded studies based on full-text is in Table 4.1 below.

Characteristics of the Included Studies

The MAs included two Cochrane reviews, by Ohlsson et al., undertaking two Cochrane series of MA updates; one series focused on ibuprofen (56, 113-118) and the other on paracetamol (98, 119-120). The current study included the last update in each (56, 98). Included MAs were recent (56, 59, 98, 122-124), published between 2011 and 2020, including four MAs (56,98,97,124) and three NMAs (59,122,123). Details of study characteristics are presented in Tables 4.2 and 4.3, including the MAs', reported pairwise comparisons.

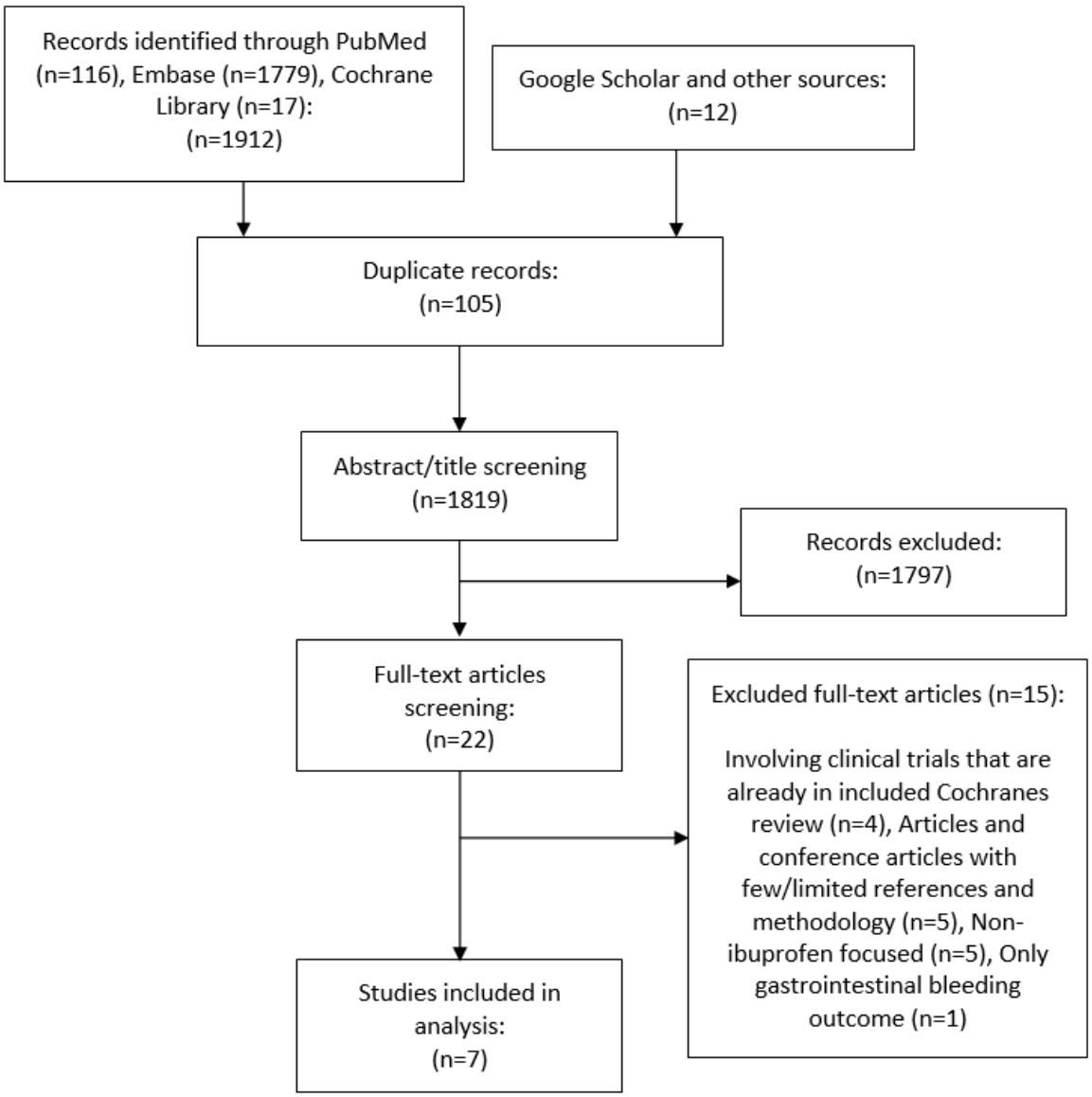

Figure 4.1. Study inclusion and exclusion flowchart

Table 4.1. Excluded Full-Text Articles

Citation	Type of study	Treatments	Reason for exclusion
Neumann R, Schulzke SM, Bührer C. Oral Ibuprofen versus Intravenous Ibuprofen or Intravenous Indomethacin for the Treatment of Patent Ductus Arteriosus in Preterm Infants: A Systematic Review and Meta-Analysis. Neonatology 2012; 102:9–15.	MA	Oral or intravenous (IV) ibuprofen (IBU), IV indomethacin (INDO)	Only 2 randomized clinical trials (RCTs) and included in Ohlsson et al. (56)
Cooke L, Steer PA, Woodgate PG. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev 2003.	MA	INDO only	INDO only
Terrin G, Conte F, Oncel MY, Scipione A, McNamara PJ, Simons S, et al. Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: a systematic review and meta-analysis. Arch Dis Child - Fetal Neonatal Ed 2016;101: F127–36.	MA	Paracetamol (APAP), INDO, IBU	All RCTs included in Ohlsson et al. [98]; the observational studies only provided APAP closure rates, with no comparison
Lu J, Li J, Li Q, Li Z. Meta-analysis to assess efficacy and safety of high-dose ibuprofen compared with standard treatment of patent ductus arteriosus in premature infants. Iran J Pediatr 2017;27.	MA	IBU only	Short article; no references; limited methodological details
Zeng YY, Xu J. Efficacy and safety of paracetamol and ibuprofen for the treatment of premature infants with patent ductus arteriosus: a Meta-analysis. Chinese J New Drugs 2019; 28:2914–20.	MA	APAP, IBU	Short article; with no references or study details
Chaiyapak R. Comparison of oral versus intravenous NSAIDs for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants: A systematic review and meta-analysis. Value Heal 2014;17: A722–3.	MA	INDO, IBU, Sulindac	Conference abstract; no references; limited methodological details
Pang YS, Prasad SA, Su DY. Paracetamol vs ibuprofen for treatment of PDA in preterms: A meta-analysis of 5 randomized controlled trials. J Hong Kong Coll Cardiol 2017;25:53.	MA	APAP, IBU	No references; limited methodological details
Das RR, Arora K, Naik SS. Efficacy and safety of paracetamol versus ibuprofen for treating patent ductus arteriosus in preterm infants: A meta-analysis. J Clin Neonatal 2014; 3:183–90.	MA	APAP, IBU	Only 2 RCTs and included in Ohlsson et al. (98)

Citation	Type of study	Treatments	Reason for exclusion
Al-Turkait A, Abramson J, Choonara I, Szatkowski L, Ojha S. Renal adverse events and gastrointestinal bleeding with ibuprofen use in preterm neonates with patent ductus arteriosus (PDA). Arch Dis Child 2019;104.	MA	APAP, INDO, IBU	Only studied GIB outcome; limited references; no list of included studies; limited methodological details
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.	MA	INDO only	INDO only
Hossain J, Shabuj M. Oral paracetamol versus intravenous paracetamol in the closure of patent ductus arteriosus: A proportion meta-analysis. J Clin Neonatol 2018; 7:121–4.	MA	APAP only	APAP only
Thomas RL, Parker GC, Van Overmeire B, Aranda J V. A meta-analysis of ibuprofen versus indomethacin for closure of patent ductus arteriosus. Eur J Pediatr 2005; 164:135–40.	MA	IBU, INDO	All RCTs included in Ohlsson et al. (56)
Herrera CM, Holberton JR, Davis PG. Prolonged versus short course of indomethacin for the treatment of patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev 2007.	Review	INDO only	INDO only
Jasani B, Weisz DE, McNamara PJ. Evidence-based use of acetaminophen for hemodynamically significant ductus arteriosus in preterm infants. Semin Perinatol 2018; 42:243–52.	MA	APAP, IBU, INDO	RCTs included in Ohlsson et al. (56, 98)

MA: Meta-analysis, RCTs: randomized controlled trails, APAP: paracetamol, INDO: indomethacin, IBU: ibuprofen, GIB: gastrointestinal bleeding

Table 4.2. Characteristics of Included Studies

Author, year	Type of study	Comparative interventions	Gestational age	Birth weight	Effects measured	Test of heterogeneity
Jones et al, 2011 [122]	NMA	INDO, IBU, PBO	23-34 weeks	≤2500 grams	RR, 95%CI	I^2, Chi^2
Huang et al., 2018 [97]	MA	APAP, IBU	25.5-33.5 weeks	952-2155 grams	RR, 95%CI	I^2, Chi^2
Ohlsson et al., 2020 [98]	MA	APAP, IBU, PBO	28 -34 weeks	No criteria on BW (≤1500 grams)	RR, RD, MD, 95%CI	I^2
Ohlsson et al., 2020 [56]	MA	IBU, INDO, PBO	≤ 37 weeks	≤2500 grams	RR, RD, MD, 95%CI	I^2
Mitra et al., 2018 [59]	NMA	APAP, IBU, INDO, PBO	25.5-33.6 weeks	≤2500 grams	OR, Mean SUCRA values, Median rank, 95%CI	I^2
Marconi et al., 2019 [121]	NMA	APAP, IBU, INDO, PBO	23-33.6 weeks	No criteria on BW	OR, 95%CI	Cochrane Q test
Loomba et al., 2015 [123]	MA	IBU, INDO	25.3±1.5, and 33.2±3.1 weeks	No criteria on BW (800±100, and 1900±500 grams)	OR, MD, 95%CI	I^2, Chi^2

GA: gestational age, BW: birth weight, RCT: randomized controlled trial, MA: meta-analysis, NMA: network meta-analysis, APAP: paracetamol/acetaminophen, IBU: ibuprofen, INDO: indomethacin, PBO: placebo or no treatment, RR: relative risk or risk ratio, RD: risk difference, MD: mean difference, OR: odds ratio, CI: confidence interval, SUCRA: surface under the cumulative ranking curve

Table 4.3. Pairwise Treatment Comparisons within Included Studies

Author, year	Type of study included in the analysis	Drug 1 and formulation[1,2,3]	Drug 2 and formulation[1,2,3]	No. of studies (of which RCTs or QRCT)	No. of infants
Ohlsson et al., 2020 [56]	RCT and QRCT	IBU (oral or IV)	INDO (oral or IV)	24 (24)	1590
		IV IBU	PBO	2 (2)	206
		Oral IBU	INDO (oral or IV)	8 (8)	272
		Oral IBU	IV IBU	5 (5)	406
		High dose IBU (oral or IV)	IBU (oral or IV)	3 (3)	190
Ohlsson et al., 2020 [98]	RCT and QRCT	Oral APAP	Oral IBU	5 (5)	559
		APAP	INDO	2 (2)	273
Marconi et al. 2019 [121]	RCT and observational studies	IBU	INDO	31 (19)	2843
		IBU	APAP	10 (9)	1036
		IBU	PBO	6 (6)	426
		APAP	INDO	2 (2)	377
Huang et al., 2018 [97]	RCT	APAP	PBO	2 (2)	117
Jones et al., 2011 [122]	RCT and QRCT	IV IBU	IV INDO	10 (10)	643
		IV INDO	PBO	9 (9)	666
		IV IBU	PBO	1 (1)	28
Loomba et al., 2015 [123]	RCT and observational studies	IBU	INDO	22 (14)	1583
Mitra et al., 2018 [59]	RCT	High dose oral IBU	Oral APAP	1 (1)	129
		High dose oral IBU	Oral IBU	2 (2)	120
		High dose IV IBU	INDO, continuous IV infusion	1 (1)	73
		High dose IV IBU	IV IBU	1 (1)	70
		Oral APAP	Oral IBU	3 (3)	327
		Oral IBU	IV INDO	4 (4)	103
		Oral IBU	INDO, other types	4 (4)	162
		Oral IBU	IV IBU	4 (4)	304
		Oral IBU	PBO or no treatment.	4 (4)	264
		IV INDO	INDO, continuous IV infusion	2 (2)	50
		IV INDO	IV IBU	12 (12)	883
		INDO	INDO, continuous IV infusion	10 (10)	802
		INDO	PBO	5 (5)	164

Author, year	Type of study included in the analysis	Drug 1 and formulation[1,2,3]	Drug 2 and formulation[1,2,3]	No. of studies (of which RCTs or QRCT)	No. of infants
		INDO, continuous IV infusion	IV IBU	1 (1)	63
		INDO, continuous IV infusion	PBO or no treatment	4 (4)	495
		IV IBU	IBU, continuous IV infusion	1 (1)	111
		IV IBU	PBO or no treatment	1 (1)	136
		INDO	INDO, continuous IV infusion	10 (10)	802

MA: meta-analysis, NMA: network meta-analysis, RCT: randomized controlled trial, QRCT: quasi-randomized controlled trial, APAP: acetaminophen/paracetamol, IBU: ibuprofen, INDO: indomethacin, PBO: placebo, IV: intravenous

[1]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis

[2]A formulation of 'oral or IV' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis

[3]Doses are standard unless stated as high doses.

Clinical Outcomes

As discussed in methods, this review's analysis includes the outcomes reported in two or more MAs. Here, based on the outcomes reported by included MAs (Table 4.4), efficacy outcomes of interest in our analysis were PDA closure, need for surgical ligation, retreatment, reopening, and duration of hospitalization, while safety outcomes were based on AEs reported, with those deemed of interest being mortality, NEC, BPD, IVH, intestinal perforation, GIB, PVL, oliguria, and elevated serum creatinine levels, ROP, sepsis, pulmonary hemorrhage, pulmonary hypertension, serum bilirubin, platelet count, and duration of ventilator support.

Table 4.4. Outcomes Reported for Pairwise Comparisons

	Marconi et al., 2019 [121]	Ohlsson et al., 2020 [98]	Ohlsson et al., 2020 [56]	Loomba et al., 2015 [123]	Jones et al., 2011 [122]	Mitra et al., 2018 [59]	Huang et al., 2018 [97]
PDA closure	yes	yes	yes	yes	yes	yes	yes
Need for surgical ligation	yes	yes	yes	yes		yes	
Need for repeat pharmacological treatment			yes			yes	
Reopening		yes	yes				
Duration of hospitalization		yes	yes				
Mortality	yes	yes	yes	yes	yes	yes	yes
NEC	yes	yes	yes	yes	yes	yes	yes
BPD	yes	CLD	CLD	yes	CLD	yes	yes
IVH	yes	yes	yes	yes	yes	yes	yes
Intestinal perforation	yes	yes	yes	yes			
GI bleeding	yes	yes	yes	yes			yes
PVL	yes	yes	yes				
Oliguria	yes	yes	yes			yes	
Serum creatinine level		yes	yes	yes			
Retinopathy of prematurity		yes	yes				yes
Sepsis		yes	yes				yes
Pulmonary hemorrhage		yes	yes				
Pulmonary hypertension		yes	yes				
Serum bilirubin		yes	yes				
Platelet count		yes	yes				
Duration of ventilator support		yes	yes				
Neurodevelopment impairment		yes					
Renal failure							yes

	Marconi et al., 2019 [121]	Ohlsson et al., 2020 [98]	Ohlsson et al., 2020 [56]	Loomba et al., 2015 [123]	Jones et al., 2011 [122]	Mitra et al., 2018 [59]	Huang et al., 2018 [97]
Time to regain birth weight			yes				
Time to full enteral feeds			yes				
AST		yes					
ALT		yes					
Deafness/ blindness		Yes					
Plasma PGE_2		yes					
Cerebral palsy		yes					

NEC: necrotizing enterocolitis, BPD: bronchopulmonary dysplasia, CLD: chronic lung disease, IVH: intraventricular hemorrhage, GI: gastrointestinal, PVL: periventricular leukomalacia, PGE_2: prostaglandin E_2

As can be seen in Table 4.5, all included studies reported the PDA closure outcome. A significant difference in performance was reported in seven pairwise comparisons, with reported superiority of oral ibuprofen over IV ibuprofen, high dose (HD) of mixed oral/IV ibuprofen formulations over standard-dose ibuprofen, HD oral ibuprofen over standard-dose IV indomethacin/ibuprofen, HD IV ibuprofen over standard-dose IV ibuprofen, oral paracetamol over IV ibuprofen.

Details of the need for surgical ligation pairwise comparisons are in Table 4.6, where superiority was reported in three comparisons to the advantage of the HD of ibuprofen against IV indomethacin/ibuprofen or oral ibuprofen.

Only one of the analyzed comparisons for neonatal mortality reported superiority, favoring mixed oral/IV formulations use of indomethacin over ibuprofen, as shown in Table 4.7.

As summarized in Table 4.8, superiority for NEC was seen in three comparisons, where oral ibuprofen performed better than IV indomethacin or the mixed oral/IV formulations of indomethacin, and the use of mixed formulations of ibuprofen was superior over the mixed formulations of indomethacin.

The superiority concerning BPD was seen in two comparisons, where IV indomethacin or its use with oral indomethacin outperformed IV ibuprofen or its use with oral ibuprofen, respectively (Table 4.9).

For IVH, in two comparisons, the outcome favored mixed oral/IV ibuprofen use over mixed oral/IV indomethacin use (Table 4.10). Mixed oral/IV use of paracetamol was associated with reduced GI bleeding in 3 comparisons (Table 4.11) compared to mixed oral/IV ibuprofen use.

The outcome of oliguria was in favor of mixed oral/IV ibuprofen over mixed oral/IV indomethacin in 3 comparisons, in favor of oral ibuprofen over IV indomethacin in one comparison, and in favor of IV ibuprofen over IV indomethacin in 2 comparisons, as illustrated in Table 4.12.

The elevation in serum creatinine levels outcome is reported in Table 14.3 and, as seen based on five comparisons, was less associated with IV ibuprofen versus IV indomethacin, oral ibuprofen versus oral indomethacin or IV ibuprofen, mixed oral/IV ibuprofen versus mixed oral/IV indomethacin, and with oral paracetamol over oral ibuprofen.

As summarized in Tables 4.14-16, no significant difference was observed between the pairwise comparisons of ROP, sepsis, and PVL, respectively. A significant difference

with intestinal perforation was reported in one pairwise comparison, with a superiority of ibuprofen over indomethacin (Table 4.17).

Efficacy and safety outcomes reported in only two MAs were combined in Table 4.18. The need for retreatment was observed to be superior in 1 comparison, where IV ibuprofen was favored over oral ibuprofen (Table 4.18). Other reported outcomes, including reopening rates, pulmonary hemorrhage, pulmonary hypertension, and duration of hospitalization, had no significant difference. A substantial increase in serum bilirubin post-treatment was observed in mixed oral/IV ibuprofen compared to oral/IV indomethacin or oral/IV paracetamol, where indomethacin or paracetamol performed better than ibuprofen. In two comparisons regarding platelet count, mixed oral/IV ibuprofen outperformed mixed oral/IV indomethacin, and mixed oral/IV paracetamol outperformed mixed oral/IV ibuprofen. The duration of ventilator support was superior in one comparison, where mixed oral/ IV ibuprofen performed better than mixed oral/IV indomethacin.

Table 4.5. Studies for Patent Ductus Arteriosus (PDA) Closure

Author, year	Drug 1 and formulation[2,3,4]	Drug 2 and formulation[2,3,4]	No. of studies and infants	Cycles of treatment for PDA closure	Effect size (95% CI)	Heterogeneity	Statistically significant difference
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	24 studies, 1590 infants	3 doses IBU of 10, 5, 5 mg/kg, 24-hours interval. INDO 0.1- 0.2 mg/kg, 12-24 hours interval	RR 1.07 (0.92, 1.24)	I^2=0%	No
	Oral IBU	INDO (oral or IV)	8 studies, 272 infants	3 doses IBU of 10, 5, 5 mg/kg, 24-hours interval. INDO 0.2 mg/kg, 12- 24 hours interval	RR 0.96 (0.73, 1.27)	I^2=0%	No
	Oral IBU	IV IBU	5 studies, 406 infants	3 doses IBU of 10, 5, 5 mg/kg, 24-hours interval for 3 days	RR 0.38 (0.26, 0.56)	I^2=0%	Yes, in favor of oral IBU
	High dose IBU (oral or IV)	IBU (oral or IV)	3 studies, 190 infants	3 high doses IBU of 20, 10, 10 mg/kg OR 15, 7.5, 7.5 mg/kg, 24-hours interval. Standard dose IBU of 10, 5, 5 mg/kg, 24-hours interval	RR 0.37 (0.22, 0.61)	I^2=4%	Yes, in favor of high dose IBU (oral or IV)
Jones et al., 2011 [122]	IV IBU	IV INDO	10 studies, 615 infants	3 doses IBU of 10, 5, 5 mg/kg, 24- hours interval. INDO 0.2 mg/kg, 12-hours interval	RR 1.00 (0.93, 1.08)	Chi^2=3.24, I^2=0%	No
Mitra et al., 2018 [59][1]	High dose oral IBU	IV INDO	Direct and indirect studies	3 doses IBU of 15, 7.5, 7.5 mg/kg OR 20, 10, 10 mg/kg, 12-24 hours interval. INDO 0.1-0.3 mg/kg	OR 2.35 (1.08, 5.31)	NA	Yes, in favor of high dose oral IBU
	IV IBU	IV INDO	12 studies, 879 infants	3 doses IBU of 10, 5, 5 mg/kg, 12-24 hours interval. INDO 0.1-0.3 mg/kg	OR 0.86 (0.59, 1.24)	NA	No

Author, year	Drug 1 and formulation[2,3,4]	Drug 2 and formulation[2,3,4]	No. of studies and infants	Cycles of treatment for PDA closure	Effect size (95% CI)	Heterogeneity	Statistically significant difference
	High dose IV IBU	IV INDO	Direct and indirect studies	3 doses	OR 2.41 (0.68, 9.86)	NA	No
	Oral IBU	IV INDO	Direct and Indirect studies	3 doses	OR 1.45 (0.94,	NA	No
	High dose oral IBU	Oral IBU	Direct and indirect studies	3 doses	OR 1.63 (0.84, 3.24)	NA	No
	High dose IV IBU	IV IBU	Direct and indirect studies	3 doses	OR 3.68 (1.09, 14.59)	NA	Yes, in favor of high dose IV IBU
	High dose oral IBU	IV IBU	Direct and indirect studies	3 doses	OR 3.59 (1.64, 8.17)	NA	Yes, in favor of high dose oral IBU
Marconi et al. 2019 [121]	IBU	INDO	31 studies	End of treatment (1-3 course cycles). The course: 3 doses IBU of 10, 5, 5 mg/kg, 24-hours interval. 3 doses INDO of 0.1-0.25 mg/kg, 12-24 hours interval, including prolonged treatment with INDO (6 doses)	OR 0.88 (0.71, 1.11)	NA	No
	IBU	INDO	Direct and indirect studies	End of treatment (1-3 cycles)	OR 0.89 (0.68, 1.17)	NA	No
Loomba et al., 2015 [123]	IV IBU	IV INDO	14 studies, 1068 infants	(1-2 cycles). 3 doses IBU of 10, 5, 5 mg/kg, 24-hours interval	OR 1.07 (0.81, 1.43)	Chi^2=6.09, I^2=0%	No

Author, year	Drug 1 and formulation[2,3,4]	Drug 2 and formulation[2,3,4]	No. of studies and infants	Cycles of treatment for PDA closure	Effect size (95% CI)	Heterogeneity	Statistically significant difference
	Oral IBU	IV INDO	6 studies,	hours interval. INDO 0.1-0.25 mg/kg, 12-24 hours interval (1-2 cycles).	OR 0.76 (0.50,	I^2=0%	No
Ohlsson et al., 2020 [98]	IBU (oral or IV)	APAP (oral or IV)	5 studies, 559 infants	(1 course). 3 doses IBU of 10, 5, 5 mg/kg, 24-hours interval. APAP 10-15 mg/kg, 6-hours interval for 3 days	RR 0.95 (0.75, 1.21)	I^2=0%	No
Huang et al., 2018 [97]	Oral IBU	Oral APAP	4 studies, 477 infants	3 doses IBU of 10, 5, 5 mg/kg, 24-hours interval for 3 days APAP 60, 60, 60 mg/day for 3 days	RR 1.02 (0.90, 1.16)	Chi^2=2.46, I^2=0%	No
Mitra et al., 2018 [59][1]	High dose oral IBU	Oral APAP	Direct and indirect studies	3 doses	OR 1.23 (0.62, 2.48)	NA	No
	High dose IV IBU	Oral APAP	Direct and indirect studies	3 doses APAP 15 mg/kg, 6-hours interval for 3, 5, 7 days	OR 1.25 (0.31, 5.77)	NA	No
	Oral IBU	Oral APAP	Direct and indirect studies	3 doses	OR 1.33 (0.81,2.17)	NA	No
	IV IBU	Oral APAP	Direct and indirect studies	3 doses	OR 2.93 (1.53, 5.62)	NA	Yes, in favor of oral APAP
	IBU, continuous IV infusion	Oral APAP	Direct and indirect studies	3 doses	OR 4.08 (1.35, 12.47)	NA	Yes, in favor of oral APAP

Author, year	Drug 1 and formulation[2,3,4]	Drug 2 and formulation[2,3,4]	No. of studies and infants	Cycles of treatment for PDA closure	Effect size (95% CI)	Heterogeneity	Statistically significant difference
Marconi et al. 2019 [121]	APAP	IBU	10 studies	End of treatment (1-3 cycles). The cycle: 3 doses IBU of 10, 5, 5 mg/kg, 24-hours interval. APAP 10-15 mg/kg, 6-hours interval for 3 days, including prolonged treatment of APAP (7 days)	OR 1.02 (0.72, 1.44)	NA	No
	APAP	IBU	Direct and indirect studies	End of treatment (1-3 cycles)	OR 1.22 (0.77, 1.91)	NA	No

RCT: randomized controlled trial, including quasi-RCT, APAP: acetaminophen/paracetamol, IBU: ibuprofen, INDO: indomethacin, PBO: placebo, IV: intravenous, RR: risk ratio, OR: odd ratio, Chi^2: Chi-square test, I^2: I-square index, NA: not available, CI: confidence interval

[1]In overall, Mitra et al reported for IV IBU in PDA closure a mean SUCRA 0.24, SD ±0.07; median rank 8, 95% CI 7-9, for high dose oral IBU a mean SUCRA 0.89, SD ±0.12; median rank 2, 95% CI 1-5, and for high dose IV IBU a mean SUCRA 0.84, SD ±0.20; median rank 2, 95% CI 1-7

[2]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis

[3]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis

[4]Doses are standard unless stated as high doses.

High dose regimen: 15-20 mg/kg/day followed by ibuprofen 7.5-10 mg/kg/day for two doses.

Table 4.6. Studies for the Need for Surgical Ligation

Author, year	Drug 1 and formulation[1,2,3]	Drug 2 and formulation[1,2,3]	No. of studies and infants	Effect size (95% CI)	Heterogeneity	Statistically significant difference
Loomba et al., 2015 [123]	IV IBU	IV INDO	9 studies, 835 infants	OR 0.86 (0.58, 1.28)	Chi^2=3.69, I^2=0%	No
	Oral IBU	IV INDO	4 studies, 342 infants	OR 0.78 (0.45, 1.37)	Chi^2=2.47, I^2=0%	No
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	16 studies, 1275 infants	RR 1.06 (0.81, 1.39)	I^2=0%	No
	Oral IBU	INDO (oral or IV)	4 studies, 174 infants	RR 0.93 (0.50, 1.74)	I^2=0%	No
	Oral IBU	IV IBU	5 studies, 406 infants	RR 0.41 (0.41, 1.21)	I^2=0%	No
	High dose IBU (oral or IV)	IBU (oral or IV)	1 study, 70 infants	RR 1.00 (0.15, 6.71)	NA	No
Marconi et al. 2019 [121]	IBU	INDO	23 studies	OR 0.9 (0.8, 1.00)	NA	No
	IBU	INDO	Indirect studies	OR 0.92 (0.79, 1.12)	NA	No
Mitra et al., 2018 [59]	High dose oral IBU	IV INDO	Indirect studies	OR 0.01 (0, 0.38)	NA	Yes, in favor of high dose oral IBU
	High dose IV IBU	IV INDO	Indirect studies	OR 1.41 (0.10, 22.80)	NA	No
	Oral IBU	IV INDO	Direct and indirect studies	OR 0.62 (0.20, 1.76)	NA	No
	IV IBU	IV INDO	Direct and indirect studies	OR 1.42 (0.79, 3.01)	NA	No
	High dose oral IBU	IV IBU	Indirect studies	OR 1.01 (0.00, 0.26)	NA	Yes, in favor of high dose oral IBU

Author, year	Drug 1 and formulation[1,2,3]	Drug 2 and formulation[1,2,3]	No. of studies and infants	Effect size (95% CI)	Heterogeneity	Statistically significant difference
	High dose IV IBU	IV IBU	Direct and indirect studies	OR 0.97 (0.07, 14.2)	NA	No
	High dose oral IBU	Oral IBU	Indirect studies	OR 0.02 (0.00, 0.50)	NA	Yes, in favor of high dose oral IBU
	High dose IV IBU	Oral IBU	Direct and indirect studies	OR 2.22 (0.14, 50.00)	NA	No
	High dose oral IBU	Oral APAP	Indirect studies	OR 0.04 (0, 2.81)	NA	No
	High dose IV IBU	Oral APAP	Indirect studies	OR 4.0 (0.1, 100)	NA	No
Ohlsson et al., 2020 [98]	APAP (oral or IV)	IBU (oral or IV)	2 studies, 290 infants	RR 0.68 (0.35, 1.32)	I^2=0%	No

RCT: randomized controlled trial, including quasi-RCT, APAP: acetaminophen/paracetamol, IBU: ibuprofen, INDO: indomethacin, PBO: placebo, IV: intravenous, RR: risk ratio, OR: odd ratio, Chi^2: Chi-square test, I^2: I-square index, NA: not available, CI: confidence interval

[1]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis

[2]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis

[3]Doses are standard unless stated as high doses.

High dose regimen: 15-20 mg/kg/day followed by ibuprofen 7.5-10 mg/kg/day for two doses.

Table 4.7. Studies for Neonatal Mortality

Author, year	Drug 1 and formulation[2,3,4]	Drug 2 and formulation[2,3,4]	No. of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	10 studies, 697 infants	RR 0.79 (0.54, 1.17)	Chi^2=7.29, I^2=0%	No
	IBU PO	INDO (oral or IV)	4 studies, 165 infants	RD -0.1 (-0.2, 0)	Chi^2=0.58, I^2=0%	No
	IBU PO	IBU IV	1 study, 64 infants	RR 1.13 (0.5, 2.55)	NA	No
	High dose IBU (oral or IV)	Standard dose IBU (oral or IV)	2 studies, 155 infants	RR 1.02 (0.58, 1.79)	Chi^2=0.36, I^2=0%	No
Jones et al., 2011 [122]	IV IBU	IV INDO	5 studies, 473 infants	RR 0.99 (0.55, 1.80)	NA	No
Mitra et al., 2018 [59][1]	High dose oral IBU	IV INDO	Direct and indirect studies	OR 2.19 (0.15, 72.38)	NA	No
	High dose IV IBU	IV INDO	Direct and indirect studies	OR 1.07 (0.27, 4.81)	NA	No
	Oral IBU	IV INDO	Direct and indirect studies	OR 0.84 (0.45, 1.53)	NA	No
	IV IBU	IV INDO	Direct and indirect studies	OR 0.91 (0.56, 1.44)	NA	No
Marconi et al. 2019 [121]	IBU	INDO	23 studies	OR 0.77 (0.67, 0.89)	NA	Yes, in favor of INDO
	IBU	INDO	Direct and indirect studies	OR 0.85 (0.70, 1.10)	NA	No
Loomba et al., 2015 [123]	IV IBU	IV INDO	9 studies, 944 infants	OR 1.03 (0.67, 1.58)	Chi^2=11.24, I^2=29%	No
Ohlsson et al., 2020 [98]	APAP (oral or IV)	IBU (oral or IV)	3 studies, 272 infants	RR 0.96 (0.55, 1.67)	I^2=0%	No

Author, year	Drug 1 and formulation[2,3,4]	Drug 2 and formulation[2,3,4]	No. of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference
Huang et al., 2018 [98]	APAP (oral or IV)	IBU (oral or IV)	3 studies, 390 infants	RR 1.45 (0.55, 3.81)	Chi^2= 3.43, I^2=42%	No
Mitra et al., 2018 [59][1]	High dose oral IBU	Oral APAP	Direct and indirect studies	OR 2.47 (0.15, 80.63)	NA	No
	High dose IV IBU	Oral APAP	Direct and indirect studies	OR 1.24 (0.25, 6.83)	NA	No
	Oral IBU	Oral APAP	Direct and indirect studies	OR 1.03 (0.49, 2.34)	NA	No
	IV IBU	Oral APAP	Direct and indirect studies	OR 0.95 (0.38, 2.52)	NA	No
	IBU, continuous IV infusion	Oral APAP	Direct and indirect studies	OR 1.09 (0.04, 45.81)	NA	No
Marconi et al. 2019 [121]	IBU	APAP	6 studies	OR 1.07 (0.62, 1.86)	NA	No
	IBU	APAP	Direct and indirect studies	OR 1.11 (0.65, 1.88)	NA	No

RCT: randomized controlled trial, including quasi-RCT, APAP: acetaminophen/paracetamol, IBU: ibuprofen, INDO: indomethacin, PBO: placebo, IV: intravenous, RR: risk ratio, OR: odd ratio, Chi^2: Chi-square test, I^2: I-square index, NA: not available, CI: confidence interval

[1]In overall, Mitra et al reported for IV IBU in neonatal mortality a mean SUCRA 0.71, SD ±0.2; median rank 3, 95% CI 1-8

[2]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.

[3]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis

[4]Doses are standard unless stated as high doses.

High dose regimen: 15-20 mg/kg/day followed by ibuprofen 7.5-10 mg/kg/day for two doses.

Table 4.8. Studies for Necrotizing Enterocolitis (NEC)

Author, year	Drug 1 and formulation[2,3,4]	Drug 2 and formulation[2,3,4]	No. of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	18 studies, 1292 infants	RR 0.68 (0.49, 0.94)	I^2=0%	Yes, in favor of IBU (oral or IV)
	Oral IBU	INDO (oral or IV)	7 studies, 249 infants	RR 0.41 (0.23, 0.73)	I^2=0%	Yes, in favor of oral IBU
	High dose IBU (oral or IV)	IBU (oral or IV)	2 studies, 130 infants	RR 1.00 (0.40, 2.50)	I^2=0%	No
Jones et al., 2011 [122]	IV IBU	IV INDO	3 studies, 473 infants	Pooled RR 0.6 (0.27, 1.33)	NA	No
Mitra et al., 2018 [59][1]	Oral IBU	IV INDO	Direct and indirect studies	OR 0.41 (0.21, 0.75)	NA	Yes, in favor of oral IBU
	High dose oral IBU	IV INDO	Direct and indirect studies	OR 0.30 (0.05, 1.72)	NA	No
	High dose IV IBU	IV INDO	Direct and indirect studies	OR 0.97 (0.17, 6.29)	NA	No
	IV IBU	IV INDO	Direct and indirect studies	OR 0.67 (0.40, 1.14)	NA	No
	IBU, continuous IV infusion	IV INDO	Direct and indirect studies	OR 0.25 (0.04, 1.21)	NA	No
Marconi et al. 2019 [121]	IBU	INDO	23 studies	OR 1.08 (0.85, 1.38)	NA	No
	IBU	INDO	Direct and indirect studies	OR 1.16 (0.88, 1.62)	NA	No
Loomba et al., 2015 [123]	IV IBU	IV INDO	8 studies, 825 infants	OR 0.97 (0.63, 1.50)	Chi^2=4.40, I^2=0%	No
	Oral IBU	IV INDO	5 studies, 391 infants	OR 0.60 (0.30, 1.24)	Chi^2=3.93, I^2=0%	No
Ohlsson et al., 2020 [98]	APAP (oral or IV)	IBU (oral or IV)	5 studies, 559 infants	RR 0.88 (0.46, 1.7)	I^2=0%	No
Huang et al., 2018 [97]	APAP (oral or IV)	IBU (oral or IV)	5 studies	RR 0.86 (0.41, 1.81)	NA	No

Author, year	Drug 1 and formulation[2,3,4]	Drug 2 and formulation[2,3,4]	No. of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference
Mitra et al., 2018 [59][1]	High dose oral IBU	Oral APAP	Direct and indirect studies	OR 0.66 (0.10, 4.24)	NA	No
	High dose IV IBU	Oral APAP	Direct and indirect studies	OR 2.16 (0.29, 18.21)	NA	No
	Oral IBU	Oral APAP	Direct and indirect studies	OR 1.12 (0.42, 2.88)	NA	No
	IV IBU	Oral APAP	Direct and indirect studies	OR 0.68 (0.23, 2.04)	NA	No
	IBU, continuous IV infusion	Oral APAP	Direct and indirect studies	OR 0.56 (0.07, 3.34)	NA	No
Marconi et al. 2019 [121]	APAP	IBU	8 studies	OR 0.99 (0.57, 1.71)	NA	No

RCT: randomized controlled trial, including quasi-RCT, APAP: acetaminophen/paracetamol, IBU: ibuprofen, INDO: indomethacin, PBO: placebo, IV: intravenous, RR: risk ratio, OR: odd ratio, Chi^2: Chi-square test, I^2: I-square index, NA: not available, CI: confidence interval.

[1]In overall, Mitra et al reported for IV IBU in NEC a mean SUCRA 0.42, SD ±0.14; median rank 6, 95% CI 4-8.

[2]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.

[3]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[4]Doses are standard unless stated as high doses.

High dose regimen: 15-20 mg/kg/day followed by ibuprofen 7.5-10 mg/kg/day for two doses.

Table 4.9. Studies for Bronchopulmonary Dysplasia (BPD) at 28 Days and/or 36 Weeks Postmenstrual Age

Author, year	Drug 1 and formulation[2,3,4]	Drug 2 and formulation[2,3,4]	No. of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	5 studies, 292 infants	RR 1.12 (0.93, 1.55) for CLD at 28 days	Chi^2= 2.58, I^2=0%	No
	IBU (oral or IV)	INDO (oral or IV)	3 studies, 357 infants	RR 1.12 (0.77, 1.61) for CLD at 36 weeks	Chi^2= 1.81, I^2=0%	No
	Oral IBU	IV IBU	3 studies, 236 infants	RR 0.82 (0.56, 1.2) at 36 weeks	Chi^2= 0.07, I^2=0%	No
	High-dose IBU	Standard-dose IBU	1 study, 70 infants	RR 1.6 (0.85, 3.02) at 36 weeks	NA	No
Jones et al., 2011 [122]	IV IBU	IV INDO	5 studies, 463 infants	RR 1.28 (1.03, 1.60),	NA	Yes, in favor of IV INDO
Mitra et al., 2018 [59][1]	High dose IV IBU	IV INDO	Direct and indirect studies	OR 2.37 (0.73, 8.02) at 36 weeks	NA	No
	Oral IBU	IV INDO	Direct and indirect studies	OR 0.68 (0.40, 1.14) at 36 weeks	NA	No
	IV IBU	IV INDO	Direct and indirect studies	OR 1.10 (0.78, 1.55) at 36 weeks	NA	No
	IBU, continuous IV infusion	IV INDO	Direct and indirect studies	OR 1.25 (0.40, 3.76) at 36 weeks	NA	No
Marconi et al. 2019 [121]	IBU	INDO	15 studies	OR 0.89 (0.81, 0.99)	NA	Yes, in favor of INDO
	IBU	INDO	Direct and indirect studies	OR 0.86 (0.71, 1.54)	NA	No
Loomba et al., 2015 [123]	IV IBU	IV INDO	6 studies, 640 infants	OR 1.09 (0.77, 1.54) for BPD at 28 days	Chi^2= 5.69, I^2=12%	No
	Oral IBU	IV INDO	4 studies, 120 infants	OR 0.80 (0.47, 1.36) for BPD at 28 days	Chi^2= 3.35, I^2=10%	No
Ohlsson et al., 2020 [98]	APAP (oral or IV)	IBU (oral or IV)	1 study, 90 infants	RR 0.79 (0.46, 1.35) at 28 days	NA	No
	APAP (oral or IV)	IBU (oral or IV)	1 study, 90 infants	RR 0.71 (0.38, 1.3) at 36 weeks	NA	No

Author, year	Drug 1 and formulation[2,3,4]	Drug 2 and formulation[2,3,4]	No. of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference
Huang et al., 2018 [97]	APAP (oral or IV)	IBU (oral or IV)	3 studies, 327 infants	RR 0.69 (0.41, 1.16)	Chi^2= 0.22 I^2=0%	No
Mitra et al., 2018 [59][1]	Oral IBU	IV IBU	Direct and indirect studies	OR 0.62 (0.36, 1.03) at 36 weeks	NA	No
	Oral APAP	IV IBU	Direct and indirect studies	OR 0.57 (0.22, 1.38) at 36 weeks	NA	No
	High dose IV IBU	IV IBU	Direct and indirect studies	OR 2.14 (0.71, 6.86) at 36 weeks	NA	No
	Oral APAP	Oral IBU	Direct and indirect studies	OR 0.92 (0.38, 2.15) at 36 weeks	NA	No
	High dose IV IBU	Oral IBU	Direct and indirect studies	OR 3.49 (1.00, 12.43) at 36 weeks	NA	No
Marconi et al. 2019 [121]	IBU	APAP	6 studies	OR 1.20 (0.56, 2.54)	NA	No
	IBU	APAP	Direct and indirect studies	OR 1.40 (0.74, 2.82)	NA	No

RCT: randomized controlled trial, including quasi-RCT, APAP: acetaminophen/paracetamol, IBU: ibuprofen, INDO: indomethacin, PBO: placebo, CLD: chronic lung disease, IV: intravenous, RR: risk ratio, OR: odd ratio, Chi^2: Chi-square test, I^2: I-square index, NA: not available, CI: confidence interval.

[1]In overall, Mitra et al reported for oral IBU in BPD a mean SUCRA 0.87 SD ±0.13; median rank 2, 95% CI 1-4.

[2]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.

[3]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[4]Doses are standard unless stated as high doses.

High dose regimen: 15-20 mg/kg/day followed by ibuprofen 7.5-10 mg/kg/day for two doses.

Table 4.10. Studies for Intraventricular Hemorrhage (IVH)

Author, year	Drug 1 and formulation[1,2,3]	Drug 2 and formulation[1,2,3]	No. of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	7 studies, 524 infants	RR 0.89 (0.61, 1.31)	Chi^2=1.49, I^2=0%	No
	IBU (oral or IV)	INDO (oral or IV)	10 studies, 798 infants	RR 1.05 (0.68, 1.63) for grade III- IV	Chi^2=3.46, I^2=0%	No
	Oral IBU	INDO (oral or IV)	3 studies, 77 infants	RD -0.03 (-0.22, 0.16)	Chi^2=0.69, I^2=0%	No
	Oral IBU	INDO (oral or IV)	2 studies, 124 infants	RD -0.04 (-0.14, 0.05) for grade III-IV	Chi^2=0.34, I^2=0%	No
	Oral IBU	IV IBU	1 study, 64 infants	RR 1.08 (0.59, 2)	NA	No
	High dose IBU	Standard dose IBU	1 study, 70 infants	RR 0.67 (0.21, 2.16)	NA	No
	High dose IBU	Standard dose IBU	1 study, 70 infants	RR 0.5 (0.1, 2.56) grade III-IV	NA	No
Jones et al., 2011 [122]	IV IBU	IV INDO	6 studies, 496 infants	RR 1.16 (0.61, 2.21)	NA	No
Mitra et al., 2018 [59]	High dose IV IBU	IV INDO	Direct and indirect studies	OR 0.53 (0.11, 2.50)	NA	No
	Oral IBU	IV INDO	Direct and indirect studies	OR 0.93 (0.51, 1.66)	NA	No
	IV IBU	IV INDO	Direct and indirect studies	OR 0.89 (0.49, 1.65)	NA	No
Marconi et al. 2019 [121]	INDO	IBU	19 studies	OR 1.25 (1.01, 1.56)	NA	Yes, in favor of IBU
	INDO	IBU	Direct and indirect studies	OR 1.27 (1.00, 1.62)	NA	Yes, in favor of IBU
Loomba et al., 2015 [123]	IV IBU	IV INDO	7 studies, 785 infants	OR 0.79 (0.47, 1.31) grade III-IV	chi^2=5.66, I^2=0%	No

Author, year	Drug 1 and formulation[1,2,3]	Drug 2 and formulation[1,2,3]	No. of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference
Ohlsson et al., 2020 [98]	APAP (oral or IV)	IBU (oral or IBU)	5 studies, 559 infants	RR 0.97 (0.77, 1.23)	chi^2=2.59, I^2=0%	No
	APAP (oral or IV)	IBU (oral or IBU)	3 studies, 272 infants	RR 1 (0.3, 3.37) for grade III-IV	chi^2=0, I^2=0%	No
Huang et al., 2018 [97]	APAP (oral or IV)	IBU (oral or IV)	5 studies, 677 infants	RR 0.84 (0.49, 1.46)	chi^2=0.79, I^2=0%	No
Mitra et al., 2018 [59]	Oral IBU	IV IBU	Direct and indirect studies	OR 1.04 (0.62, 1.77)	NA	No
	Oral APAP	IV IBU	Direct and indirect studies	1.14 (0.50, 2.59)	NA	No
	High dose IV IBU	IV IBU	Direct and indirect studies	0.59 (0.14, 2.45)	NA	No
	Oral APAP	Oral IBU	Direct and indirect studies	OR 1.09 (0.54, 2.22)	NA	No
	High dose IV IBU	Oral IBU	Direct and indirect studies	OR 0.57 (0.12, 2.64)	NA	No
Marconi et al. 2019 [121]	IBU	APAP	9 studies	OR 0.98 (0.58, 1.64)	NA	No
	IBU	APAP	Direct and indirect studies	OR 0.99 (0.63, 1.60)	NA	No

RCT: randomized controlled trial, including quasi-RCT, APAP: acetaminophen/paracetamol, IBU: ibuprofen, INDO: indomethacin, PBO: placebo, IV: intravenous RR: risk ratio, OR: odd ratio, Chi^2: Chi-square test, I^2: I-square index, NA: not available, CI: confidence interval.

[1]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.

[2]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[3]Doses are standard unless stated as high doses.

High dose IBU regimen: 15-20 mg/kg/day followed by ibuprofen 7.5-10 mg/kg/day for two doses.

Table 4.11. Studies for Gastrointestinal Bleeding (GIB)

Author, year	Drug 1 and formulation[1,2,3]	Drug 2 and formulation[1,2,3]	No. of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference
Marconi et al. 2019 [121]	IBU	INDO	8 studies	OR 1.03 (0.61, 1.76)	NA	No
	IBU	INDO	Direct and indirect studies	OR 0.87 (0.39, 2.07)	NA	No
Loomba et al., 2015 [123]	IV IBU	IV INDO	4 studies, 317 infants	OR 1.40 (0.73, 2.69)	No significant heterogeneity	No
	Oral IBU	IV INDO	3 studies, 313 infants	OR 0.62 (0.31, 1.27	Chi^2=2.75, I^2=27%	No
Ohlsson et al., 2018 [98]	IBU (oral or IV)	INDO (Oral or IV)	7 studies, 514 infants	RR 0.94 (0.55, 1.61)	Chi^2=3.51, I^2=0%	No
	Oral IBU	INDO (Oral or IV)	3 studies, 85 infants	RD 0.07 (-0.05, 0.18)	Chi^2=0.73, I^2=0%	No
	Oral IBU	IV IBU	2 studies, 172 infants	RR 2.89 (0.12, 69.24)	NA	No
	High dose IBU (oral or IV)	Standard IBU (oral or IV)	2 studies, 120 infants	RR 1.5 (0.58, 3.86)	Chi^2=0.07, I^2=0%	No
Ohlsson et al., 2018 [56]	APAP (oral or IV)	IBU (oral or IV)	4 studies, 537 infants	RR 0.28 (0.12, 0.69)	I^2=0	Yes, in favor of oral or IV APAP
Huang et al., 2018 [97]	APAP	IBU	4 studies, 527 infants	RR 0.28 (0.11, 0.73)	Chi^2=0.88, I^2=0%	Yes, in favor of APAP
Marconi et al. 2019 [121]	IBU	APAP	5 studies	OR 3.51 (1.36, 9.08)	NA	Yes, in favor of APAP
	IBU	APAP	Direct and indirect studies	OR 2.94 (0.94, 11.81)	NA	No

RCT: randomized controlled trial, including quasi-RCT, APAP: acetaminophen/paracetamol, IBU: ibuprofen, INDO: indomethacin, PBO: placebo, IV: intravenous, RR: risk ratio, OR: odd ratio, Chi^2: Chi-square test, I^2: I-square index, NA: not available, CI: confidence interval.
[1]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.
[2]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.
[3]Doses are standard unless stated as high doses.
High dose regimen: 15-20 mg/kg/day followed by ibuprofen 7.5-10 mg/kg/day for two doses.

Table 4.12 Studies for Oliguria

Author, year	Drug 1 and formulation[2,3,4]	Drug 2 and formulation[2,3,4]	No. of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	6 studies, 576 infants	RR 0.28 (0.14, 0.54)	I^2=24%	Yes, in favor of IBU (oral or IV)
	Oral IBU	IV IBU	4 studies, 304 infants	RR 0.14 (0.01, 2.66)	NA	No
	High dose IBU (oral or IV)	IBU (oral or IV)	2 studies, 120 infants	RR 1.57 (0.44, 5.63)	I^2=0%	No
Mitra et al., 2018 [59]	Oral IBU	IV INDO	Direct and indirect studies	OR 0.20 (0.04, 0.92)	NA	Yes, in favor of oral IBU
	IV INDO	IV IBU	Direct and indirect studies	OR 0.29 (0.18, 0.46)	NA	Yes, in favor of IV IBU
	IV INDO	IBU, continuous IV infusion	Direct and indirect studies	OR 0.02 (0.00, 0.52)	NA	Yes, in favor of IBU, continuous IV infusion
	IV INDO	High dose IV IBU	Direct and indirect studies	OR 0.47 (0.06, 3.88)	NA	No
Marconi et al. 2019 [121]	INDO	IBU	12 studies	OR 3.29 (1.80, 6.00)	NA	Yes, in favor of IBU
	INDO	IBU	Direct and indirect studies	OR 3.92 (1.69, 9.82)	NA	Yes, in favor of IBU
Ohlsson et al., 2020 [56]	APAP (oral or IV)	IBU (oral or IV)	3 studies, 337 infants	RR 0.46 (0.2, 1.1)	I^2=33.24%	No
Mitra et al., 2018 [59]	Oral APAP	Oral IBU	Direct and indirect studies	OR 0.55 (0.22, 1.27)	NA	No
	Oral APAP	IV IBU	Direct and indirect studies	OR 0.35 (0.07, 1.98)	NA	No
Marconi et al. 2019 [121]	APAP	IBU	2 studies	OR 2.45 (0.63, 9.54)	NA	No
	IBU	APAP	Direct and indirect studies	OR 2.75 (0.57, 18.38)	NA	No

RCT: randomized controlled trial, including quasi-RCT, APAP: acetaminophen/paracetamol, IBU: ibuprofen, INDO: indomethacin, PBO: placebo, IV: intravenous, RR: risk ratio, OR: odd ratio, Chi^2: Chi-square test, I^2: I-square index, NA: not available, CI: confidence interval.

[1]In overall, Mitra et al reported for oral IBU in oliguria a mean SUCRA 0.60, SD ±0.19; median rank 4, 95% CI 2-7.

[2]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.

[3]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[4]Doses are standard unless stated as high doses.

High dose regimen: 15-20 mg/kg/day followed by ibuprofen 7.5-10 mg/kg/day for two doses.

Table 4.13 Studies for Serum Creatinine Level

Author, year	Drug 1 and formulation[1,2,3]	Drug 2 and formulation[1,2,3]	No. of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference
Loomba et al., 2015 [123]	IV IBU	IV INDO	7 studies, 655 infants	MD -0.08 (-0.16, 0.00)	Chi^2=1244.0, I^2=100%	Yes, in favor of IV IBU
	Oral IBU	IV INDO	5 studies, 272 infants	MD -0.03 (-0.11, 0.05)	Chi^2= 4.09, I^2=2%	No
	Oral IBU	Oral INDO	2 studies, 103 infants	MD -0.1 (-0.13, -0.07)	Chi^2= 0.22, I^2=0%	Yes, in favor of oral IBU
Ohlsson et al., 2020 [56]	Oral APAP	Oral IBU	4 studies, 537 infants	MD -8.92 (-11.28,-6.55)	I^2=84%	Yes, in favor of oral APAP
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	11 studies, 918 infants	MD -8.12 (-10.81, -5.43)	I^2=83%	Yes, in favor of IBU
	Oral IBU	INDO (oral or IV)	5 studies, 190 infants	MD -0.51 (-6.04, 5.01)	I^2=72%	No
	Oral IBU	IV IBU	2 studies, 170 infants	MD -22.47 (-32.40, -12.53)	I^2=81%	Yes, in favor of oral IBU
	High dose IBU (oral or IV)	IBU (oral or IV)	1 study, 60 infants	MD 8.84 (-4.41, 22.09)	Not applicable	No

RCT: randomized controlled trial, including quasi-RCT, APAP: acetaminophen/paracetamol, IBU: ibuprofen, INDO: indomethacin, PBO: placebo, IV: intravenous, RR: risk ratio, OR: odd ratio, MD: mean difference, Chi^2: Chi-square test, I^2: I-square index, NA: not available, CI: confidence interval.
[1]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.
[2]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.
[3]Doses are standard unless stated as high doses.

Table 4.14. Studies for Retinopathy of Prematurity

Author, year	Drug 1 and formulation[1,2,3]	Drug 2 and formulation[1,2,3]	No. of studies and infants	Outcome effect and size (95% CI)	Heterogeneity	Statistically significant difference
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	7 studies, 581 infants	RR 0.81 (0.6, 1.1)	Chi^2=1.51, I^2=0%	No
	Oral IBU	INDO (oral or IV)	2 studies, 71 infants	RD 0(-0.81, 0.17)	Chi^2=0.38, I^2=0%	No
	Oral IBU	IV IBU	2 studies, 172	RR 0.59(0.26, 1.34) required laser treatment	Chi^2=0.56, I^2=0%	No
	High dose IBU	Standard dose IBU	1 study, 70 infants	RR 1(0.27,3.69)	NA	No
	High dose IBU	Standard dose IBU	1 study, 70 infants	RR 2(0.19, 21.06) stage 3-4	NA	No
Ohlsson et al., 2020 [56]	APAP (oral or IV)	IBU (oral or IV)	4 studies, 472 infants	RR 0.71 (0.42, 1.23)	Chi^2= 0.05, I^2=0%	No
	APAP (oral or IV)	IBU (oral or IV)	1 study, 90 infants	RR 0.71 (0.12, 1.55) grade 3-4	NA	No
Huang et al., 2018 [97]	APAP	IBU	4 studies, 580 infants	RR 0.58 (0.28, 1.21)	Chi^2= 1.94, I^2=0%	No

RCT: randomized controlled trial, including quasi-RCT, APAP: acetaminophen/paracetamol, IBU: ibuprofen, INDO: indomethacin, PBO: placebo, IV: intravenous, RR: risk ratio, OR: odd ratio, MD: mean difference, Chi^2: Chi-square test, I^2: I-square index, NA: not available, CI: confidence interval.
[1]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.
[2]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.
[3]Doses are standard unless stated as high doses.

Table 4.15. Studies for Sepsis

Author, year	Drug 1 and formulation[1,2,3]	Drug 2 and formulation[1,2,3]	No. of studies and infants	Outcome effect and size (95% CI)	Heterogeneity	Statistically significant difference
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	7 studies, 735 infants	RR 1.22 (0.84, 1.76)	Chi^2= 1.33, I^2=0%	No
	Oral IBU	INDO (oral or IV)	2 studies, 53 infants	RR 0.03 (-0.22, 0.28)	Chi^2= 0.08, I^2=0%	No
	Oral IBU	IV IBU	3 studies, 236 infants	RR 0.82 (0.54, 1.25)	Chi^2= 1.68, I^2=0%	No
Ohlsson et al., 2020 [56]	APAP (oral or IV)	IBU (oral or IV)	4 studies, 472 infants	RR 0.88 (0.64, 1.21)	Chi^2= 1.19, I^2=0%	No
Huang et al., 2018 [97]	APAP	IBU	4 studies, 590 infants	RR 0.88 (0.62, 1.25)	Chi^2= 1.50, I^2=0%	No

RCT: randomized controlled trial, including quasi-RCT, APAP: acetaminophen/paracetamol, IBU: ibuprofen, INDO: indomethacin, PBO: placebo, IV: intravenous, RR: risk ratio, OR: odd ratio, MD: mean difference, Chi^2: Chi-square test, I^2: I-square index, NA: not available, CI: confidence interval.
[1]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.
[2]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.
[3]Doses are standard unless stated as high doses.

Table 4.16 Studies for Periventricular Leukomalacia

Author, year	Drug 1 and formulation[1,2,3]	Drug 2 and formulation[1,2,3]	No. of studies and infants	Outcome effect and size (95% CI)	Heterogeneity	Statistically significant difference
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	6 studies, 573 infants	RR 1.24 (0.67, 2.3)	Chi^2= 3.18, I^2=0%	No
	Oral IBU	INDO (oral or IV)	1 study, 41 infants	RR -0.05 (-0.18, 0.08)	NA	No
	Oral IBU	IV IBU	1 study, 64 infants	RR 1 (0.15, 6.67)	NA	No
	High dose IBU	Standard dose IBU	1 study, 70 infants	RR 1.5 (0.27, 8.43)	NA	No
Marconi et al., 2019 [121]	IBU	INDO	7 studies	OR 0.83 (0.53, 1.30)	NA	No
	IBU	INDO	Direct and indirect studies	OR 0.90 (0.53, 1.61)	NA	No
Ohlsson et al., 2020 [56]	APAP (oral or IV)	IBU (oral or IV)	3 studies, 272 infants	RR 1 (0.36, 2.76)	Chi^2= 0.43, I^2=0%	No

RCT: randomized controlled trial, including quasi-RCT, APAP: acetaminophen/paracetamol, IBU: ibuprofen, INDO: indomethacin, PBO: placebo, IV: intravenous, RR: risk ratio, OR: odd ratio, RD: risk difference, MD: mean difference, Chi^2: Chi-square test, I^2: I-square index, NA: not available, CI: confidence interval.
[1]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.
[2]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.
[3]Doses are standard unless stated as high doses. High dose regimen: 15-20 mg/kg/day followed by ibuprofen 7.5-10 mg/kg/day for two doses.

Table 4.17. Studies for Intestinal Perforation

Author, year	Drug 1 and formulation[1,2,3]	Drug 2 and formulation[1,2,3]	No. of studies and infants	Outcome effect and size (95% CI)	Heterogeneity	Statistically significant difference
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	5 studies, 255 infants	RR 0.48 (0.2, 1.14)	Chi^2= 2.61, I^2=0%	No
	Oral IBU	INDO (oral or IV)	2 studies, 62 infants	RR -0.1 (-0.25, 0.04)	Chi^2= 1.61, I^2=37.91%	No
	Oral IBU	IV IBU	2 studies, 134 infants	RR 0.32 (0.01, 7.48)	NA	No
Marconi et al., 2019 [121]	IBU	INDO	11 studies	OR 0.51 (0.38, 0.68)	NA	Yes, in favor of IBU
	IBU	INDO	Direct and indirect studies	OR 0.58 (0.36, 1.11)	NA	No
Loomba et al., 2015 [123]	IV IBU	IV INDO	7 studies, 762 infants	OR 1.09 (0.54, 2.20)	Chi^2= 3.09, I^2=0%	No
Ohlsson et al., 2020 [56]	APAP (oral or IV)	IBU (oral or IV)	1 study, 90 infants	NA	NA	NA

RCT: randomized controlled trial, including quasi-RCT, APAP: acetaminophen/paracetamol, IBU: ibuprofen, INDO: indomethacin, PBO: placebo, IV: intravenous, RR: risk ratio, OR: odd ratio, RD: risk difference, MD: mean difference, Chi^2: Chi-square test, I^2: I-square index, NA: not available, CI: confidence interval.

[1]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.

[2]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[3]Doses are standard unless stated as high doses.

Higher doses regimen: 20 mg/kg/day followed by ibuprofen 10 mg/kg/day for two doses.

Table 4.18. Pairwise Comparisons for Need for Re-treatment, Re-opening Rate, Pulmonary Hypertension, Serum Bilirubin Post Treatment, Platelet Counts, Duration of Hospitalization, and Ventilator Support

Author, year	Drug 1 and formulation[1,2,3]	Drug 2 and formulation[1,2,3]	No. of studies and infants	Outcome, and effect size (95% CI)	Heterogeneity	Statistically significant difference
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	7 studies, 241 infants	Re-treatment, RR 1.2 (0.76, 1.9)	Chi^2= 3.37, I^2=0%	No
Mitra et al., 2018 [59]	IV IBU	IV INDO	7 studies, 518 infants	Re-treatment, OR 1.36 (0.80, 2.15)	NA	No
	PO IBU	IV INDO	3 studies, 85 infants	Re-treatment, OR 0.96 (0.34, 3.65)	NA	No
	PO IBU	IV IBU	3 studies, 240 infants	Re-treatment, OR 0.34 (0.16, 0.61)	NA	Yes, in favor of PO IBU
	PO APAP	PO IBU	2 studies, 240 infants	Re-treatment, OR 0.92 (0.47, 1.76)	NA	No
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	7 studies, 305 infants	Re-opening, RR 1.57 (0.83, 2.99)	Chi^2= 0.82, I^2=0%	No
	PO IBU	INDO (oral or IV)	1 study, 20 infants	Re-opening, RD 0 (-0.17, 0.17)	NA	No
	High dose IBU (oral or IV)	Standard dose IBU (oral or IV)	1 study, 70 infants	Re-opening, RR 2 (0.39, 10.22)	NA	No
Ohlsson et al., 2020 [56]	APAP (oral or IV)	IBU (oral or IV)	2 studies, 143 infants	Re-opening, RR 1.04 (0.5, 2.18)	Chi^2= 0.96, I^2=0%	No
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	4 studies, 303 infants	Pulmonary hemorrhage, RR 0.91(0.4, 2.04)	Chi^2= 3.84, I^2=21.89%	No
	Oral IBU	INDO (oral or IV)	1 study, 21 infants	Pulmonary hemorrhage, RD -0.22(-0.51, 0.07)	NA	No
	Oral IBU	IV IBU	1 study, 70 infants	Pulmonary hemorrhage, RR 0.14(0.01, 2.52)	NA	No
Ohlsson et al., 2020 [56]	APAP (oral or IV)	IBU (oral or IV)	3 studies, 312 infants	Pulmonary hemorrhage, RR 0.63(0.23, 1.74)	Chi^2= 0.65, I^2=0%	No

Author, year	Drug 1 and formulation[1,2,3]	Drug 2 and formulation[1,2,3]	No. of studies and infants	Outcome, and effect size (95% CI)	Heterogeneity	Statistically significant difference
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	2 studies, 118 infants	Pulmonary hypertension, RR 3.53 (0.15, 81.11)	NA	No
	Oral IBU	INDO (oral or IV)	1 study, 83 infants	Pulmonary hypertension, RD 0 (-0.05, 0.05)	NA	No
Ohlsson et al., 2020 [56]	APAP (oral or IV)	IBU (oral or IV)	1 study, 90 infants	Pulmonary hypertension, RR 0.33 (0.01, 7.97)	NA	No
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	1 study, 200 infants	Serum bilirubin (mmol/L) after treatment, MD 12.65 (9.96, 15.34)	NA	Yes, in favor of INDO
Ohlsson et al., 2020 [56]	APAP (oral or IV)	IBU (oral or IV)	2 studies, 290 infants	Serum bilirubin (mmol/L) after treatment, MD -11.25 (-13.88, -8.62)	Chi^2= 1.63, I^2=38.55%	Yes, in favor of APAP
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	1 study, 200 infants	Platelet count ($X10^9$/L), MD 72 (58.07, 85.93)	NA	Yes, in favor of IBU
	High-dose IBU (oral or IV)	Standard-dose IBU (oral or IV)	1 study, 60 infants	Platelet count ($X10^9$/L), MD -29 (-74.83, 16.83)	NA	No
Ohlsson et al., 2020 [56]	APAP (oral or IV)	IBU (oral or IV)	2 studies, 287 infants	Platelet count ($X10^9$/L), MD 30.18 (16.55, 43.81)	Chi^2= 12.1, I^2=91.74%	Yes, in favor of APAP
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	4 studies, 368 infants	Duration of hospitalization, MD -0.69 (-4.54, 3.16)	Chi^2= 3.43, I^2=12.49%	No
Ohlsson et al., 2020 [56]	APAP (oral or IV)	IBU (oral or IV)	1 study, 90 infants	Duration of hospitalization, MD -6.5 (-21.42, 8.42)	NA	No
Ohlsson et al., 2020 [56]	IBU (oral or IV)	INDO (oral or IV)	6 studies, 471 infants	Duration of ventilator support, MD -2.35 (-3.71,-0.99)	Chi^2= 6.18, I^2=19.07%	Yes, in favor of IBU
	Oral IBU	IV IBU	2 studies, 134 infants	Duration of ventilator support, MD 0.54 (-0.01, 1.1)	Chi^2= 1.1, I^2=9.5%	No

Author, year	Drug 1 and formulation[1,2,3]	Drug 2 and formulation[1,2,3]	No. of studies and infants	Outcome, and effect size (95% CI)	Heterogeneity	Statistically significant difference
Ohlsson et al., 2020 [56]	APAP (oral or IV)	IBU (oral or IV)	1 study, 90 infants	Duration of ventilator support, MD -4.15 (-8.63, 0.33)	NA	No

RCT: randomized controlled trial, including quasi-RCT, APAP: acetaminophen/paracetamol, IBU: ibuprofen, INDO: indomethacin, PBO: placebo, IV: intravenous, RR: risk ratio, OR: odd ratio, RD: risk difference, MD: mean difference, Chi^2: Chi-square test, I^2: I-square index, NA: not available, CI: confidence interval.

[1]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.

[2]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[3]Doses are standard unless stated as high doses.

High dose regimen: 15-20 mg/kg/day followed by ibuprofen 7.5-10 mg/kg/day for two doses.

Quality of Methods Assessment

Based on the AMSTAR-2 assessment of the four studies, the quality of methods was assessed to be low in three MAs (97, 121, 122), critically low in one MA (123), moderate in one study (59), and high in the 2 Cochrane studies (56, 98). Assessment items were studies underperformed can be seen in Figure 4.2.

Risk of Bias Assessment

Based on the ROBIS assessment, the risk of bias was determined to be high in two studies (97, 123) and unclear in two studies (121, 122) and low in three studies (56, 59, 98). Domains of ROBIS where studies underperformed were identifying and selecting studies, data collection and study appraisal, and the synthesis and findings (Figure 4.3).

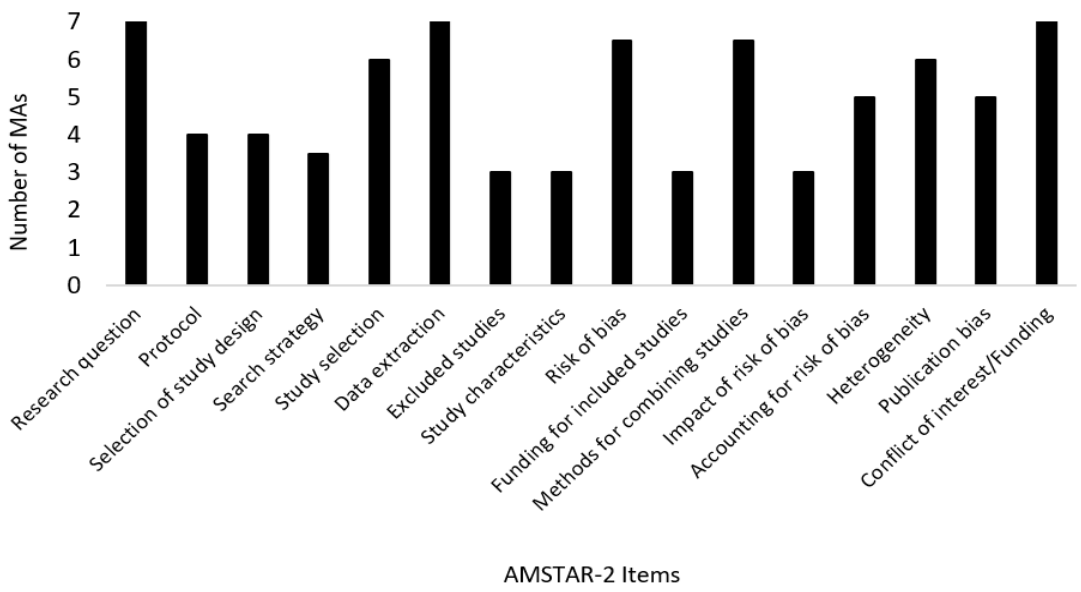

Figure 4.2. Quality of methods

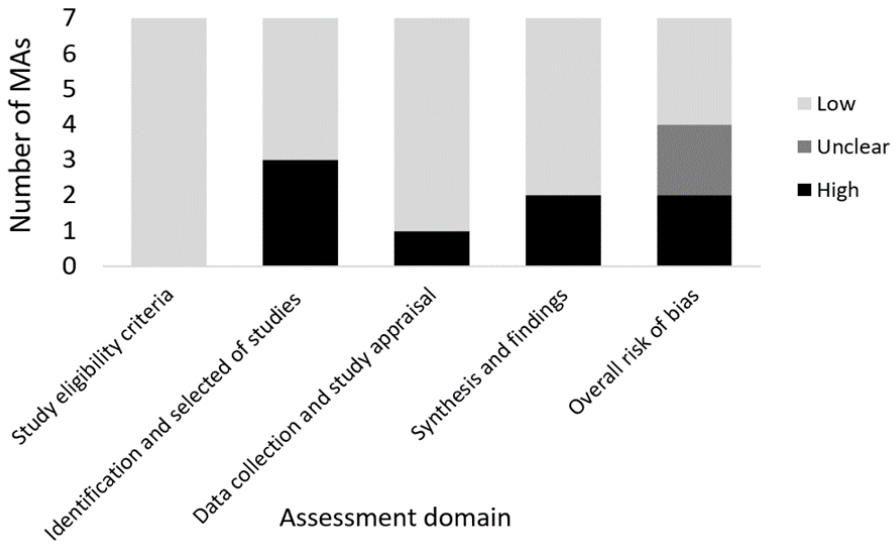

Figure 4.3. Risk of bias

Phase Two: Cost-effectiveness Analysis of Ibuprofen versus Indomethacin or Paracetamol for the Treatment of PDA in Preterm Neonates

Base-case Clinical Outcome for Ibuprofen versus Indomethacin

The relative success of PDA closure based on the decision tree model with each treatment strategy was as seen in Table 4.19.

Table 4.19. Base-case Outcome for Success of PDA Closure

Treatment	Effect (Success of PDA) (95% confidence interval)
Oral ibuprofen	0.9034 (0.8238- 0.9510)
IV indomethacin	0.7546 (0.6534-0.8312)
IV ibuprofen	0.7256 (0.6320- 0.8139)

The mean difference in the therapy success between oral ibuprofen and IV indomethacin was 0.1488 (95% CI, 0.0865-0.2353) in favor of oral ibuprofen, while the mean difference in therapy success between IV ibuprofen and IV indomethacin was 0.02899 (95% CI, 0.0062-0.0852) in favor of IV indomethacin.

Base-case Economic Outcome for Ibuprofen versus Indomethacin

The base case total cost of each study drug is reported in Table 4.20. The mean savings in the cost of treatment between oral ibuprofen and IV indomethacin was QAR 14,484 (95% CI, 12,627-16,342) in favor of oral ibuprofen. While the mean savings in the cost of treatment between IV ibuprofen and IV indomethacin was QAR 1,450 (95% CI, 499-3,399) in favor of IV ibuprofen.

Table 4.20. Clinical Outcomes and Cost of Consequences of Oral Ibuporfen, IV Indomethacin, and IV Ibuprofen (Ibuprofen versus Indomethacin Model).

PDA treatment strategy	Outcome event	Cost (QAR) of health state	Proportional cost (QAR) of health state	Average cost (QAR) per outcome category	Total average cost (QAR) of oral ibuprofen (95% CI)
Oral ibuprofen	**Success**			373,914.2	QAR 414,761.3 (413,528- 415,994)
	PDA closure without adverse events	358,467.14	192,717.13		
	PDA closure with PVL	467,447.34	46,086.79		
	PDA closure with ROP	450,167.34	32,402.17		
	PDA closure with BPD	529,221.11	102,708.12		
	Failure			40,847.1	
	No response to first course with second course	437,684.81	4,804.55		
	No response to first course with surgical ligation	659,495.26	3,452.67		
	Death	358,467.14	5,574.27		
	Premature discontinuation with pulmonary hemorrhage	428,189.50	575.99		
	Premature discontinuation with IVH	431,961.34	7,390.43		
	Premature discontinuation with NEC	457,341.39	3,111.72		
	Premature discontinuation with GIB	399,504.15	14,410.52		
	Premature discontinuation with intestinal perforation	458,451.33	1,263.37		
	Premature discontinuation with oliguria	342,598.95	263.62		

PDA treatment strategy	Outcome event	Cost (QAR) of health state	Proportional cost (QAR) of health state	Average cost (QAR) per outcome category	Total average cost (QAR) of IV indomethacin (95% CI)
IV indomethacin	**Success**			327,228	QAR 436,158 (434,762- 437,554)
	PDA closure without adverse events	365,126.11	128,186.10		
	PDA closure with PVL	474,106.31	20,639.68		
	PDA closure with ROP	456, 826.31	83,813.12		
	PDA closure with BPD	535,880.09	94,589.06		
	Failure			108,930	
	No response to first course with second course	453,222.91	17,605.04		
	No response to first course with surgical ligation	666,154.23	18,717.06		
	Death	365,126.11	12,674.36		
	Premature discontinuation with pulmonary hemorrhage	432,628.31	6,241.05		
	Premature discontinuation with IVH	436,400.16	10,393.02		
	Premature discontinuation with NEC	461,780.21	8,547.53		
	Premature discontinuation with GIB	403,942.97	10,708.22		
	Premature discontinuation with intestinal perforation	462,890.14	12,179.80		
	Premature discontinuation with oliguria	347,037.76	11,863.95		

PDA treatment strategy	Outcome event	Cost (QAR) of health state	Proportional cost (QAR) of health state	Average cost (QAR) per outcome category	Total average cost (QAR) of IV ibuprofen (95% CI)
IV ibuprofen	**Success**			313,015	QAR 435,794 (434,427- 437,163)
	PDA closure without adverse events	360,677.17	122,793.54		
	PDA closure with PVL	469,657.38	26,148.53		
	PDA closure with ROP	452,377.38	63,048.69		
	PDA closure with BPD	531,431.15	101,024.21		
	Failure			122,779.3	
	No response to first course with second course	442,104.88	28,142.31		
	No response to first course with surgical ligation	661,705.30	21,705.60		
	Death	360,677.17	15,277.42		
	Premature discontinuation with pulmonary hemorrhage	429,846.65	9,337.58		
	Premature discontinuation with IVH	433,618.49	15,550.45		
	Premature discontinuation with NEC	458,998.54	8,210.00		
	Premature discontinuation with GIB	401,161.30	11,320.11		
	Premature discontinuation with intestinal perforation	460,108.48	8,958.14		
	Premature discontinuation with oliguria	344,256.10	4,277.72		

CI: confidence interval, QAR: Qatari Riyal, PVL: periventricular leukomalacia, ROP: retinopathy of prematurity, BPD: bronchopulmonary dysplasia, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, GIB: gastrointestinal bleeding.

As seen in Figure 4.4, the resource category that contributed most to the overall patient cost was the hospitalization, followed by the monitoring of clinical events. The cost of hospitalization was higher with IV indomethacin compared to oral ibuprofen (QAR 393,116 versus QAR 378,671). The cost of hospitalization with IV ibuprofen was higher than that with IV indomethacin (QAR 396,727 versus QAR 393,115). The IV indomethacin group was associated with a higher acquisition cost compared to oral ibuprofen (QAR 6,686 versus QAR 1.5) and compared to IV ibuprofen (QAR 6,686 versus QAR 2,277). For other resource categories, the cost minimally differed between the study drugs. An overview of the cost components for each treatment therapy is presented in Figure 4.4. The detailed costs of each clinical event are summarized based on the different cost categories in Table 4.21.

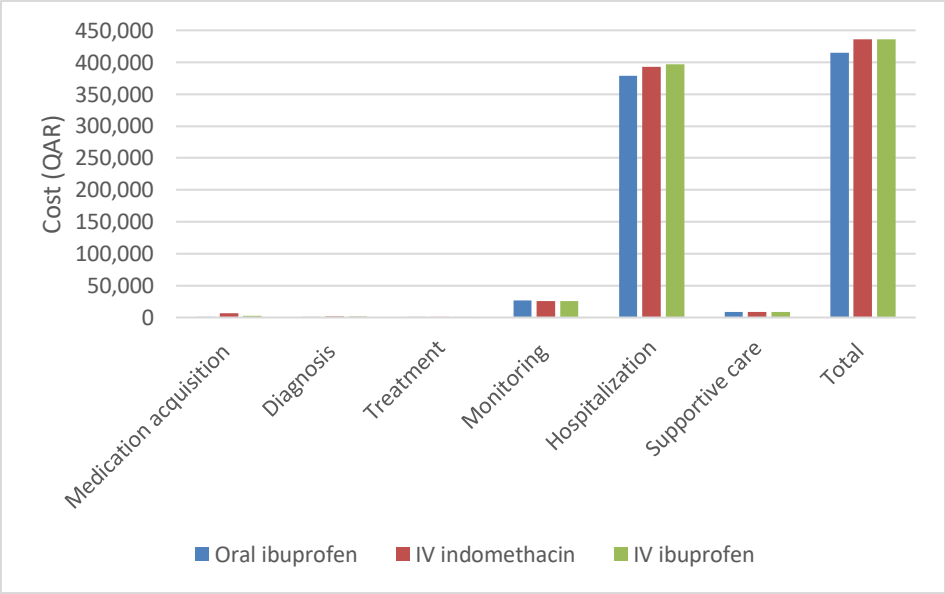

Figure 4.4. The relative value of cost components for each of the study drugs (ibuprofen versus indomethacin model)

Table 4.21. A Detailed Breakdown of Cost Components for the Different Treatments (Ibuprofen versus Indomethacin Model)

Clinical outcomes	Oral ibuprofen (QAR)	IV indomethacin (QAR)	IV ibuprofen (QAR)
PDA closure without adverse events			
Medication acquisition	0.81	2338.32	752.92
Diagnosis	239.91	156.66	151.92
Treatment	0.00	0.00	0.00
Monitoring	13,620.19	8,894.27	8,625.20
Hospitalization	176,272.70	115,109.73	111,627.44
Supportive care	2,583.43	1,687.03	1,635.99
Total	192,717.03	128,186.02	122,793.48
PDA closure with PVL			
Medication acquisition	0.10	289.96	123.13
Diagnosis	89.17	56.01	71.62
Treatment	0.00	0.00	0.00
Monitoring	1,817.12	1,141.22	1,459.51
Hospitalization	28,512.93	17,907.21	22,901.64
Supportive care	1,982.84	1,245.30	1,592.62
Total	32,402.07	20,639.69	26,148.53

Clinical outcomes	Oral ibuprofen (QAR)	IV indomethacin (QAR)	IV ibuprofen (QAR)
PDA closure with ROP			
Medication acquisition	0.15	1221.99	308.23
Diagnosis	219.74	393.80	299.15
Treatment	147.42	264.19	200.70
Monitoring	3,115.79	5,583.76	4,241.71
Hospitalization	42,111.72	75,467.75	57,329.17
Supportive care	491.96	881.63	669.73
Total	46,086.79	83,813.13	63,048.69
PDA closure with BPD			
Medication acquisition	0.29	1,175.66	420.41
Diagnosis	173.28	157.60	169.73
Treatment	0.00	0.00	0.00
Monitoring	6,578.05	5,982.77	6,443.29
Hospitalization	94,003.15	85,496.45	92,077.44
Supportive care	1,953.36	1,776.59	1,913.34
Total	102,708.12	94,589.06	101,024.21

Clinical outcomes	Oral ibuprofen (QAR)	IV indomethacin (QAR)	IV ibuprofen (QAR)
No response to first course with second course			
Medication acquisition	0.0220	603.66	281.55
Diagnosis	9.8009	34.68	56.83
Treatment	0.0000	0.00	0.00
Monitoring	304.7439	1,078.37	1,767.17
Hospitalization	4,384.4694	15,514.99	25,424.99
Supportive care	105.4984	373.31	611.77
Total	4,804.5345	17,605.02	28,142.31
No response to first course with surgical ligation			
Medication acquisition	0.01	187.14	72.54
Diagnosis	4.67	25.09	29.29
Treatment	48.12	258.27	301.52
Monitoring	167.82	900.68	1,051.52
Hospitalization	3,179.44	17,063.57	19,921.15
Supportive care	52.60	282.30	329.58
Total	3,452.67	18,717.06	21,705.59

Clinical outcomes	Oral ibuprofen (QAR)	IV indomethacin (QAR)	IV ibuprofen (QAR)
Death			
Medication acquisition	0.02	231.20	93.68
Diagnosis	6.94	15.49	18.90
Treatment	0.00	0.00	0.00
Monitoring	393.96	879.42	1,073.11
Hospitalization	5,098.62	11,381.44	13,888.18
Supportive care	74.72	166.80	203.54
Total	5,574.27	12,674.35	15,277.41
Premature discontinuation with pulmonary hemorrhage			
Medication acquisition	0.00	64.05	36.03
Diagnosis	3.65	39.14	58.93
Treatment	0.00	0.02	0.03
Monitoring	4.32	46.35	69.80
Hospitalization	553.32	5,933.94	8,935.55
Supportive care	14.69	157.55	237.24
Total	575.99	6,241.04	9,337.57
Premature discontinuation with IVH			
Medication acquisition	0.03	105.74	59.48
Diagnosis	57.71	80.32	120.96
Treatment	29.67	41.30	62.18
Monitoring	95.95	133.56	201.11

Clinical outcomes	Oral ibuprofen (QAR)	IV indomethacin (QAR)	IV ibuprofen (QAR)
Hospitalization	7,037.61	9,796.19	14,751.48
Supportive care	169.47	235.90	355.23
Total	7,390.42	10,393.01	15,550.44
Premature discontinuation with NEC			
Medication acquisition	0.01	82.18	29.67
Diagnosis	19.61	53.36	51.56
Treatment	19.05	51.83	50.09
Monitoring	137.33	373.61	361.04
Hospitalization	2,798.72	7,613.87	7,357.53
Supportive care	136.98	372.65	360.11
Total	3,111.71	8,547.52	8,209.99
Premature discontinuation with GIB			
Medication acquisition	0.05	117.70	46.80
Diagnosis	94.61	69.53	74.01
Treatment	0.53	0.39	0.41
Monitoring	319.96	235.1460	250.3063
Hospitalization	13,332.19	97,98.0678	10,429.7655
Supportive care	663.18	487.3799	518.8021
Total	14,410.52	10,708.2126	11,320.1038

Clinical outcomes	Oral ibuprofen (QAR)	IV indomethacin (QAR)	IV ibuprofen (QAR)
Premature discontinuation with intestinal perforation			
Medication acquisition	0.00	116.8276	32.2933
Diagnosis	7.94	75.8548	56.1278
Treatment	24.14	230.4976	170.5539
Monitoring	42.25	403.3993	298.4903
Hospitalization	1,133.54	10,823.3788	8,008.6251
Supportive care	55.48	529.7415	391.9756
Total	1,263.36	12,179.6995	8,958.0660
Premature discontinuation with oliguria			
Medication acquisition	0.00	151.7873	20.6104
Diagnosis	3.55	157.6028	57.2852
Treatment	0.00	0.0000	0.0000
Monitoring	4.08	181.2744	65.8893
Hospitalization	252.29	11,208.9944	4,074.2243
Supportive care	3.70	164.2773	59.7112
Total	263.6	11,863.9362	4,277.7203
Total average cost per patient of study drug	414,761	436,158	435,794

PVL: periventricular leukomalacia, ROP: retinopathy of prematurity, BPD: bronchopulmonary dysplasia, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, GIB: gastrointestinal bleeding.

Base-case Cost-effectiveness Outcomes of Oral Ibuprofen versus IV Indomethacin

The ICER of oral ibuprofen versus IV indomethacin was calculated using the following process:

$$\text{ICER}=\frac{Cost\ (QAR) of\ IV\ indomethacin - cost\ (QAR)\ of\ oral\ ibuprofen}{success\ of\ IV\ indomethacin - success\ of\ oral\ ibuprofen}$$

$$\text{ICER}=\frac{436{,}158-414{,}761}{0.7546-0.9034}=\text{negative value}$$

With a lower cost and a higher rate of success, oral ibuprofen is on average dominant over IV indomethacin, and no ICER would need to be calculated. The dominance of oral ibuprofen over IV indomethacin was maintained in 59% of the simulated cases, and oral ibuprofen was considered cost-effective in 33% of the cases. Based on the WTP threshold, there was only a 7% probability that oral ibuprofen was not cost-effective than IV indomethacin. The ICER probability curve with oral ibuprofen can be seen in Figure 4.5.

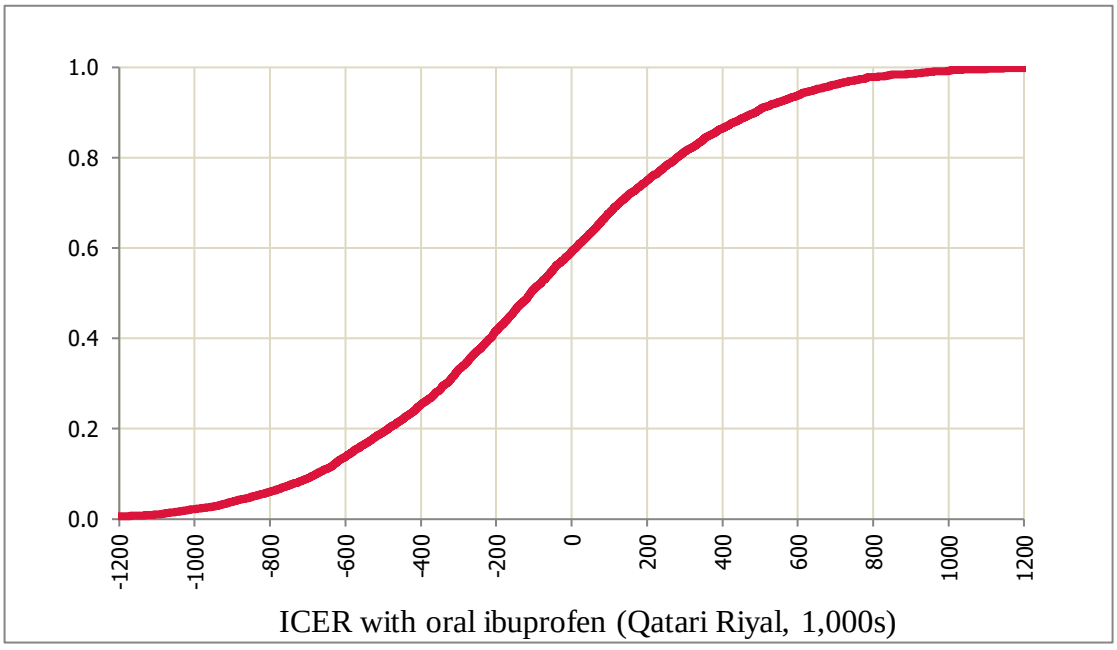

Figure 4.5. Incremental cost-effectiveness ratio (ICER, Qatari Riyal/success) acceptability curve for oral ibuprofen versus IV indomethacin

A tornado analysis of the ranking of different clinical inputs based on the strength of the relationship with the ICER is presented in Figure 4.6. The outcome with the strongest association with the ICER is the probability of success with BPD >36 weeks with either oral ibuprofen or IV indomethacin. This was followed by success with no AEs of oral ibuprofen then success with ROP >II of IV indomethacin.

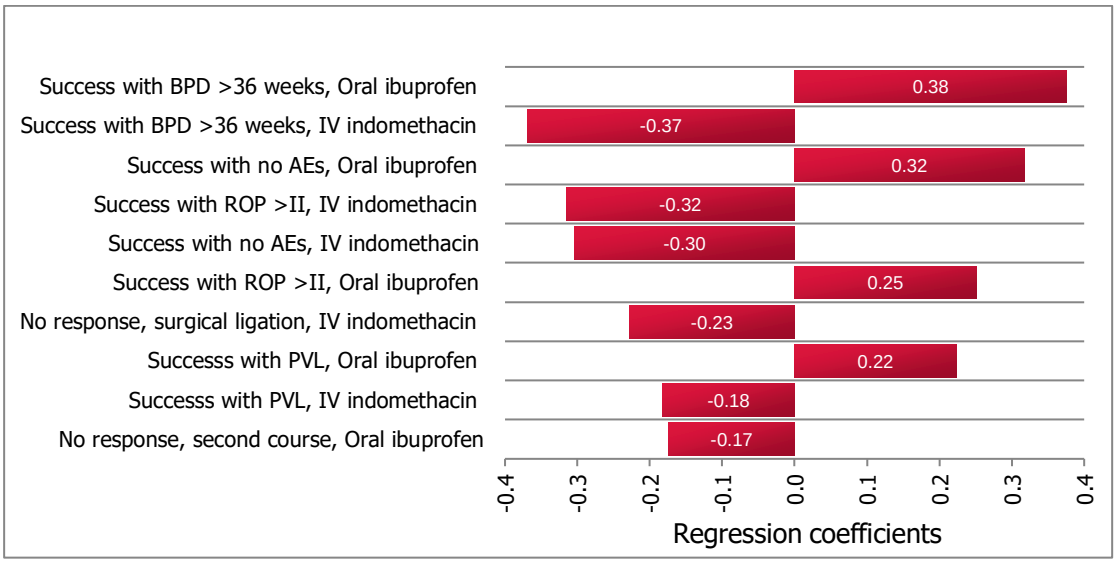

Figure 4.6. Tornado diagram of the impact of model events on the incremental cost-effectiveness ratio (oral ibuprofen versus IV indomethacin model)

Base-case Cost-effectiveness Outcomes of IV Ibuprofen versus IV Indomethacin

The ICER of IV ibuprofen versus IV indomethacin was calculated using the following process:

$$\text{ICER}=\frac{Cost\ (QAR)\ of\ IV\ indomethacin-cost\ (QAR) of\ IV\ ibuprofen}{success\ of\ IV\ indomethacin-success\ of\ IV\ ibuprofen}$$

$$\text{ICER}=\frac{436{,}158-435{,}794}{0.7546-0.7256}=$$ QAR 12,546 (-54,693- 79,785) with IV indomethacin.

On average, IV indomethacin was cost-effective compared to IV ibuprofen. However, this was maintained in only 9% of cases. IV indomethacin was dominant over IV ibuprofen in 50% of the cases, while in 41% of the cases, IV indomethacin was not cost-effective compared to IV ibuprofen. The ICER probability curve of IV ibuprofen versus IV indomethacin is presented in Figure 4.7.

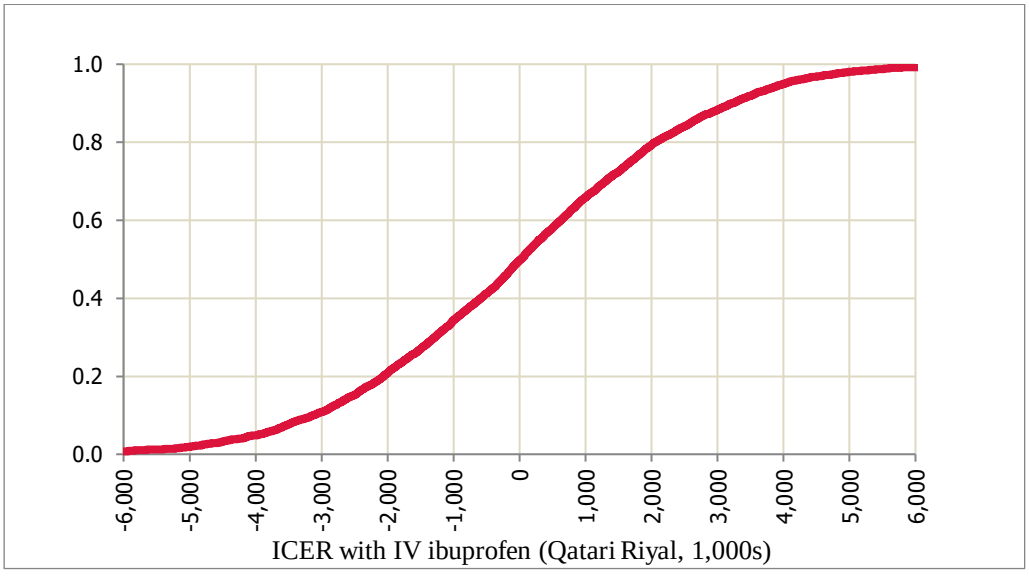

Figure 4.7. Incremental cost-effectiveness ratio (ICER, Qatari Riyal/success) acceptability curve for IV ibuprofen versus IV indomethacin

Based on the tornado analysis, the model outcome 'success with BPD >36 weeks' with either IV ibuprofen and IV indomethacin was the outcome that has the highest strength of association (regression coefficient) with the ICER, followed by success with ROP >II and success with no AEs both for IV indomethacin. A tornado graph of the analysis is presented in Figure 4.8.

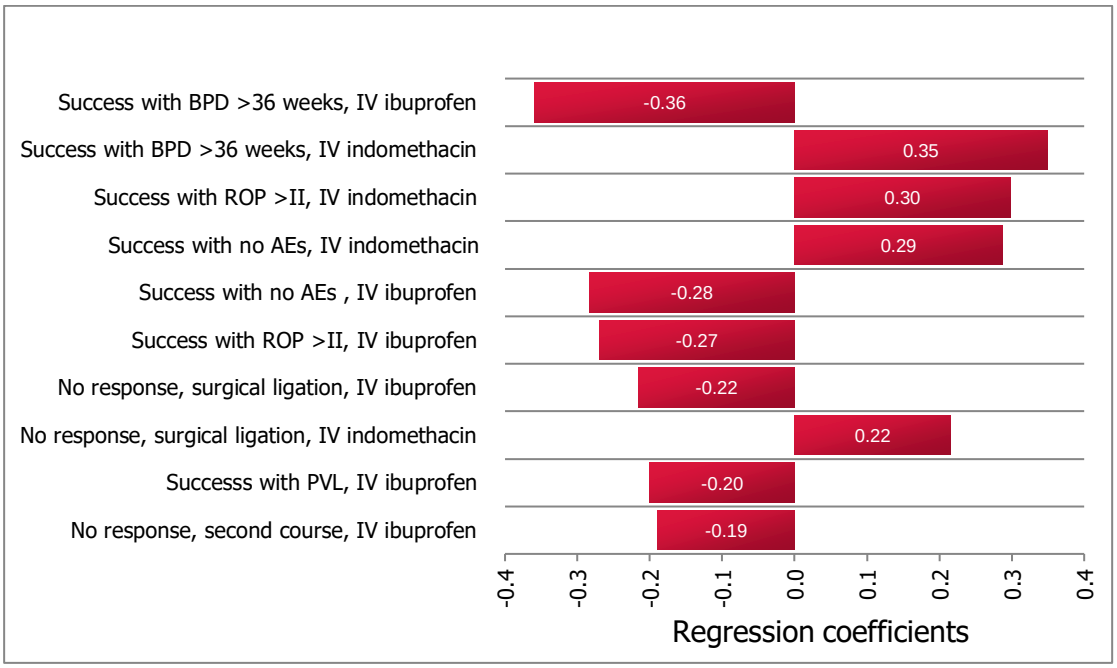

Figure 4.8. Tornado diagram of the impact of model events on the incremental cost-effectiveness ratio (IV ibuprofen versus IV indomethacin model)

Base-case Clinical Outcome of Ibuprofen versus Paracetamol

The relative success of PDA closure was 0.6258 with oral ibuprofen, 0.6327 with oral paracetamol, and 0.4706 with IV ibuprofen, Table 4.22.

Table 4.22. Base-case Outcome of Success for PDA Closure

Treatment	Total cost (95% Confidence interval)
Oral ibuprofen	0.6258 (0.5276-0.7244)
Oral paracetamol	0.6327 (0.5276-0.7244)
IV ibuprofen	0.4706 (0.3694-0.5724)

The mean difference in the therapy success between oral ibuprofen and oral paracetamol was 0.0069 (95% CI, 0.0002-0.0545) in favor of oral paracetamol, while the mean difference in therapy success between IV ibuprofen and oral paracetamol was 0.1620 (95% CI, 0.0943-0.2468) in favor of oral paracetamol.

Base-case Economic Outcome for Ibuprofen versus Paracetamol

The total cost of each study drug is calculated in Table 4.23. The mean savings in the cost of treatment between oral ibuprofen and oral paracetamol was QAR 7,172 (95% CI, 5,448-8,896) in favor of oral paracetamol. The mean savings in the cost of treatment between IV ibuprofen and oral paracetamol was QAR 17,790 (95% CI, 16,001-19,579) in favor of IV ibuprofen.

Table 4.23. Clinical Outcomes and Cost of Consequences of Oral Ibuporfen, Oral Paracetamol and IV Ibuprofen (Ibuprofen Versus Paracetamol Model)

PDA treatment strategy	Outcome event	Cost (QAR) of health state	Proportional cost (QAR) of health state	Average cost (QAR) per outcome category	Total average cost (QAR) of oral ibuprofen (95% CI)
Oral ibuprofen	**Success**			246,361.46	404,970 (403,775-406,165)
	PDA closure without adverse events	358,467.14	157,644.22		
	PDA closure with PVL	467,447.34	15,280.53		
	PDA closure with ROP	450,167.34	43,819.97		
	PDA closure with BPD	529,221.11	29,616.74		
	Failure			158,608.51	
	No response to first course with second course	437,684.81	61,475.27		
	No response to first course with surgical ligation	659,495.26	14,530.16		
	Death	358,467.14	23,760.14		
	Premature discontinuation with pulmonary hemorrhage	428,189.50	13,414.90		
	Premature discontinuation with IVH	431,961.34	6,817.03		
	Premature discontinuation with NEC	457,341.39	10,680.23		
	Premature discontinuation with GIB	399,504.15	14,080.73		
	Premature discontinuation with intestinal perforation	458,451.33	912.47		
	Premature discontinuation with oliguria	342,598.95	12,937.58		

PDA treatment strategy	Outcome event	Cost (QAR) of health state	Proportional cost (QAR) of health state	Average cost (QAR) per outcome category	Total average cost (QAR) of oral paracetamol (95% CI)
Oral paracetamol	**Success**			242,044.4	397,798 (396,571-399,025)
	PDA closure without adverse events	358,468.43	183,442.08		
	PDA closure with PVL	467,448.63	15,448.66		
	PDA closure with ROP	450,168.63	19,049.91		
	PDA closure with BPD	529,222.40	24,103.79		
	Failure			155,753.5	
	No response to first course with second course	437,687.39	73,126.38		
	No response to first course with surgical ligation	659,409.55	9,192.36		
	Death	358,468.43	26,008.80		
	Premature discontinuation with pulmonary hemorrhage	428,190.79	13,950.25		
	Premature discontinuation with IVH	431,962.63	7,775.33		
	Premature discontinuation with NEC	457,081.68	13,255.37		
	Premature discontinuation with GIB	399,505.44	5,593.08		
	Premature discontinuation with intestinal perforation	458,452.62	0.00		
	Premature discontinuation with oliguria	342,600.24	6,852.00		

PDA treatment strategy	Outcome event	Cost (QAR) of health state	Proportional cost (QAR) of health state	Average cost (QAR) per outcome category	Total average cost (QAR) of IV ibuprofen (95% CI)
IV ibuprofen	**Success**			192,573	415,588 (414,256-416,920)
	PDA closure without adverse events	360,677.17	97,614.10		
	PDA closure with PVL	469,657.38	11,546.91		
	PDA closure with ROP	452,377.38	56,134.00		
	PDA closure with BPD	531,431.15	27,277.99		
	Failure			223,015.3	
	No response to first course with second course	442,104.88	80,635.74		
	No response to first course with surgical ligation	661,705.30	20,455.33		
	Death	360,677.17	14,368.16		
	Premature discontinuation with pulmonary hemorrhage	429,846.65	47,984.16		
	Premature discontinuation with IVH	433,618.49	3,164.89		
	Premature discontinuation with NEC	458,998.54	6,217.47		
	Premature discontinuation with GIB	401,161.30	2,440.54		
	Premature discontinuation with intestinal perforation	460,108.48	1,427.57		
	Premature discontinuation with oliguria	344,256.10	46,321.40		

CI: confidence interval, QAR: Qatari riyal, PVL: periventricular leukomalacia, ROP: retinopathy of prematurity, BPD: bronchopulmonary dysplasia, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, GIB: gastrointestinal bleeding.

Similar to the ibuprofen versus indomethacin model, the resource category that contributed the most to the patient cost in the ibuprofen versus paracetamol model was the hospitalization, followed by the monitoring of clinical events. Oral ibuprofen was associated with a higher hospitalization cost compared to oral paracetamol (QAR 371,211 versus QAR 364,304). The IV ibuprofen was also associated with a higher hospitalization cost compared to oral paracetamol (QAR 381,575 versus QAR 364,305). For the acquisition cost, this was higher with IV ibuprofen compared to oral paracetamol (QAR 2,462 versus QAR 2.79). For oral ibuprofen, the cost of acquisition was similar to oral paracetamol. However, the cost of monitoring tests was higher with oral paracetamol and oral ibuprofen than IV ibuprofen (QAR 24,650, QAR 24, 346 and QAR 21,569, respectively). The costs of the other resource categories were minimally different between the study drugs. An overview of the cost components for each treatment therapy is presented in Figure 4.9. The detailed costs of each clinical event are summarized in Table 4.24.

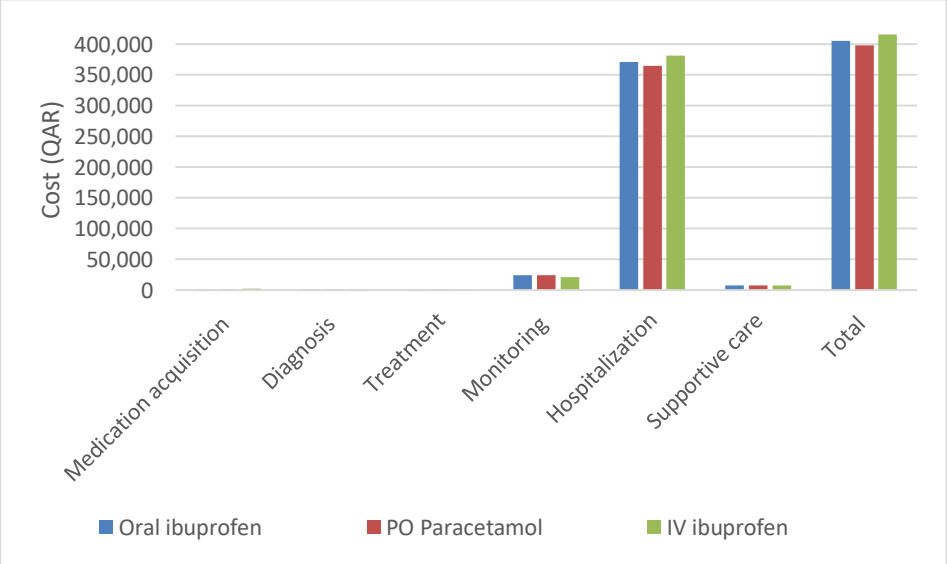

Figure 4.9. The relative value of cost components for each of the study drugs

Table 4.24. A Detailed Breakdown of Cost Components for the Different Treatments (Ibuprofen versus Paracetamol Model)

Clinical outcomes	Oral ibuprofen (QAR)	Oral paracetamol (QAR)	IV ibuprofen (QAR)
PDA closure without adverse events			
Medication acquisition	0.66	1.43	598.53
Diagnosis	196.25	228.36	120.77
Treatment	0.00	0.00	0.00
Monitoring	11,141.43	12,964.64	6,856.56
Hospitalization	144,192.54	167,788.48	88,737.66
Supportive care	2,113.26	2,459.08	1,300.53
Total	**157,644.15**	**18,3441.99**	**97,614.05**
PDA closure with PVL			
Medication acquisition	0.05	0.09	54.37
Diagnosis	42.05	42.51	31.63
Treatment	0.00	0.00	0.00
Monitoring	856.93	866.36	644.51
Hospitalization	13,446.41	13,594.32	10,113.12
Supportive care	935.09	945.3753	703.29
Total	**15,280.53**	**15,448.66**	**11,546.91**

Clinical outcomes	Oral ibuprofen (QAR)	Oral paracetamol (QAR)	IV ibuprofen (QAR)
PDA closure with ROP			
Medication acquisition	0.15	0.12	274.42
Diagnosis	208.94	90.83	266.34
Treatment	140.17	60.94	178.68
Monitoring	2,962.54	1,287.91	3,776.52
Hospitalization	40,040.41	17,406.77	51,041.75
Supportive care	467.76	203.35	596.28
Total	**43,819.97**	**19,049.91**	**56,133.99**
PDA closure with BPD			
Medication acquisition	0.08	0.12	113.52
Diagnosis	49.97	40.66	45.83
Treatment	0.00	0.00	0.00
Monitoring	1,896.83	1,543.75	1,739.78
Hospitalization	27,106.59	22,060.84	24,862.23
Supportive care	563.27	458.42	516.63
Total	**29,616.74**	**24,103.79**	**27,277.98**

Clinical outcomes	Oral ibuprofen (QAR)	Oral paracetamol (QAR)	IV ibuprofen (QAR)
No response to first course with second course			
Medication acquisition	0.28	0.47	806.72
Diagnosis	125.40	149.17	162.85
Treatment	0.00	0.00	0.00
Monitoring	3,899.27	4638.25	5,063.45
Hospitalization	56,100.29	66732.32	7,2849.82
Supportive care	1,349.88	1605.70	1,752.90
Total	**61,475.1289**	**73,125.9100**	**80,635.7423**
No response to first course with surgical ligation			
Medication acquisition	0.0330	0.0389	68.3652
Diagnosis	19.6713	12.4465	27.6004
Treatment	202.5204	128.1392	284.1528
Monitoring	706.2657	446.8701	990.9490
Hospitalization	13,380.3015	8,466.0163	18,773.6662
Supportive care	221.3657	140.0630	310.5943
Total	**14,530.1576**	**9,193.5740**	**20,455.3279**

Clinical outcomes	Oral ibuprofen (QAR)	Oral paracetamol (QAR)	IV ibuprofen (QAR)
Death			
Medication acquisition	0.0994	0.2024	88.0999
Diagnosis	29.5781	32.3772	17.7768
Treatment	0.0000	0.0000	0.0000
Monitoring	1,679.2370	1,838.1536	1,009.2409
Hospitalization	21,732.7029	23,789.4030	13,061.6069
Supportive care	318.5112	348.6539	191.4289
Total	**23,760.1286**	**26,008.7901**	**1,4368.1535**
Premature discontinuation with pulmonary hemorrhage			
Medication acquisition	0.0470	0.0909	185.1565
Diagnosis	84.9915	88.3830	302.8367
Treatment	0.0373	0.0388	0.1328
Monitoring	100.6612	104.6780	358.6700
Hospitalization	12,887.0014	13,401.2492	45,918.1942
Supportive care	342.1557	355.8092	1,219.1486
Total	**13,414.8941**	**13,950.2491**	**47,984.1389**

Clinical outcomes	Oral ibuprofen (QAR)	Oral paracetamol (QAR)	IV ibuprofen (QAR)
Premature discontinuation with IVH			
Medication acquisition	0.0237	0.0502	12.1061
Diagnosis	53.2281	60.7104	24.6174
Treatment	27.3653	31.2120	12.6561
Monitoring	88.5031	100.9440	40.9316
Hospitalization	6,491.5865	7,404.1123	3,002.2814
Supportive care	156.3220	178.2963	72.2971
Total	**6,817.0287**	**7,775.3252**	**3,164.8897**
Premature discontinuation with NEC			
Medication acquisition	0.0350	0.0809	22.4676
Diagnosis	67.3216	23.0962	39.0496
Treatment	65.3924	81.2055	37.9306
Monitoring	471.3665	628.1110	273.4143
Hospitalization	9,605.9550	11,928.8475	5,571.8967
Supportive care	470.1556	583.8477	272.7119
Total	**10,680.2263**	**13,255.0000**	**6,217.4709**
Premature discontinuation with GIB			
Medication acquisition	0.0529	0.0391	10.0907
Diagnosis	92.4434	36.7198	15.9565
Treatment	0.5163	0.2051	0.0891
Monitoring	312.6397	124.1848	53.9644
Hospitalization	13,027.0776	5,174.5326	2,248.5892

Clinical outcomes	Oral ibuprofen (QAR)	Oral paracetamol (QAR)	IV ibuprofen (QAR)
Supportive care	647.9987	257.3939	111.8503
Total	**14,080.7286**	**5,593.0752**	**2,440.5403**
Premature discontinuation with intestinal perforation			
Medication acquisition	0.0030	0.0000	5.1463
Diagnosis	5.7378	0.0000	8.9445
Treatment	17.4353	0.0000	27.1795
Monitoring	30.5140	0.0000	47.5675
Hospitalization	818.7036	0.0000	1,276.2557
Supportive care	40.0708	0.0000	62.4653
Total	**912.4645**	**0.0000**	**1,427.5587**
Premature discontinuation with oliguria			
Medication acquisition	0.0566	0.0558	223.1798
Diagnosis	174.0918	92.2022	620.3137
Treatment	0.0000	0.0000	0.0000
Monitoring	200.2401	106.0508	713.4836
Hospitalization	12,381.7270	6557.5874	44,117.8305
Supportive care	181.4647	96.1070	646.5842
Total	**12,937.5803**	**6,852.0032**	**46,321.3918**
Total average cost per patient of study drug	**QAR404,970**	**QAR397,798**	**QAR415,588**

PVL: periventricular leukomalacia, ROP: retinopathy of prematurity, BPD: bronchopulmonary dysplasia, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, GIB: gastrointestinal bleeding.

Base-case Cost-effectiveness Outcomes of Oral Ibuprofen versus Oral Paracetamol

The ICER of oral ibuprofen versus oral paracetamol was calculated using the following process:

$$\text{ICER}=\frac{Cost\ (QAR)\ of\ oral\ paracetamol-cost\ (QAR)\ of\ oral\ ibuprofen}{success\ of\ oral\ paracetamol-success\ of\ oral\ ibuprofen}$$

$$\text{ICER}=\frac{397{,}798-404{,}970}{0.6327-0.6258}=\text{negative value}$$

Oral paracetamol is on average dominant over oral ibuprofen, with a lower cost and a higher rate of success. The dominance of oral paracetamol over oral ibuprofen was maintained in 63% of the cases, and oral paracetamol was considered cost-effective in 19% of the cases. In 18% of the cases, oral paracetamol was not cost-effective over oral ibuprofen. The ICER probability curve of oral ibuprofen versus oral paracetamol is presented in Figure 4.10.

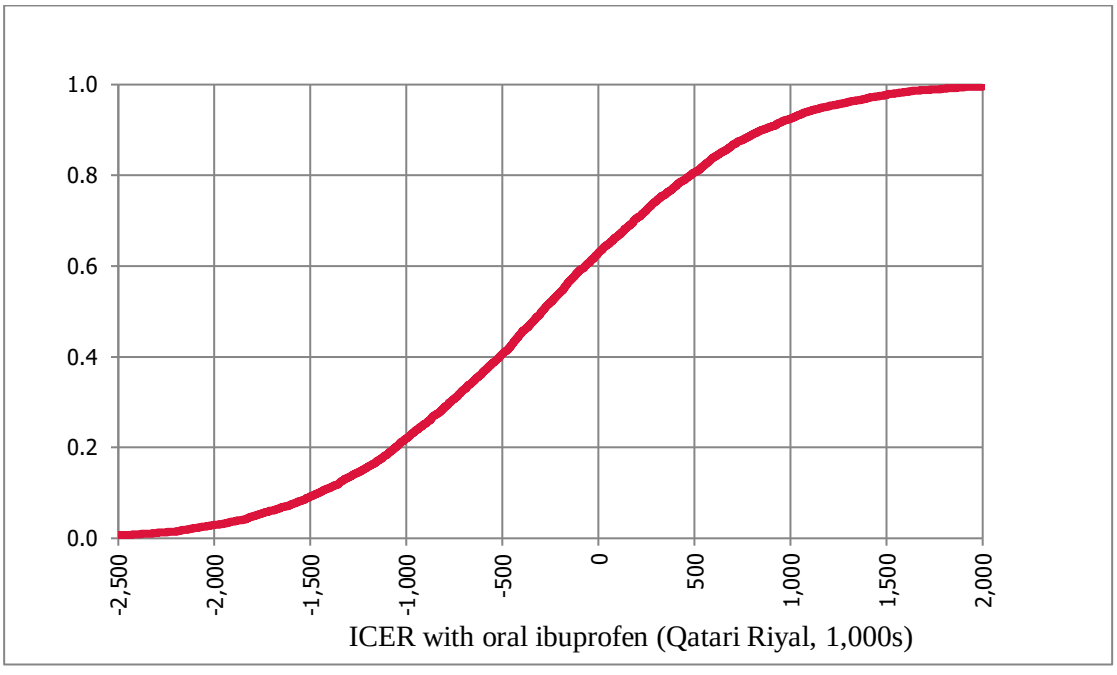

Figure 4.10. Incremental cost-effectiveness ratio (ICER, Qatari Riyal/success) acceptability curve for oral ibuprofen versus oral paracetamol

The tornado analysis of the regression coefficient shows that the outcome that has the strongest association with ICER is the probability of success with no AEs for oral paracetamol, followed by the no response to first course, with a second course, for oral paracetamol. A diagram of the analysis can be seen in Figure 4.11.

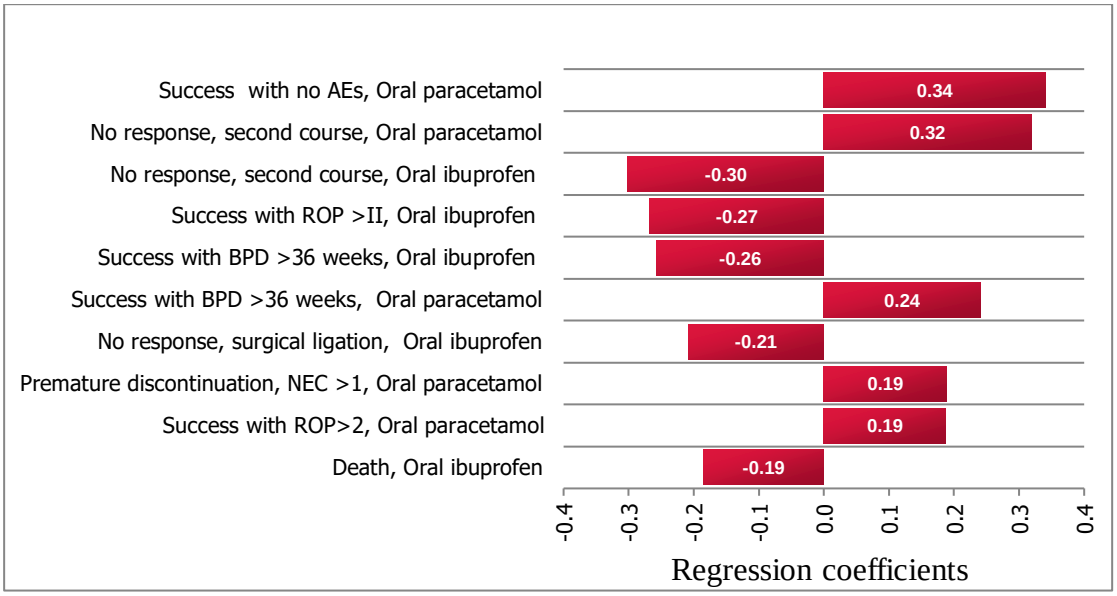

Figure 4.11. Tornado diagram of the impact of model events on incremental cost-effectiveness ratio (oral ibuprofen versus oral paracetamol model)

Base-case Cost-effectiveness Outcomes of IV Ibuprofen versus Oral Paracetamol

The ICER of IV ibuprofen versus oral paracetamol was calculated using the following process:

$$\text{ICER}=\frac{Cost\ (QAR)\ of\ oral\ paracetamol-cost\ (QAR)\ of\ IV\ ibuprofen}{success\ of\ oral\ paracetamol-success\ of\ IV\ ibuprofen}$$

$$\text{ICER}=\frac{397{,}798-415{,}588}{0.6327-0.4706}=\text{negative value}$$

Oral paracetamol is dominant over IV ibuprofen, with a lower cost and a higher rate of success, which was maintained in 52% of the simulated cases. Oral paracetamol was cost-effective in 39% of the cases. In 9% of the cases, it was not cost-effective over IV ibuprofen. The ICER probability curve of IV ibuprofen versus oral paracetamol is presented in Figure 4.12.

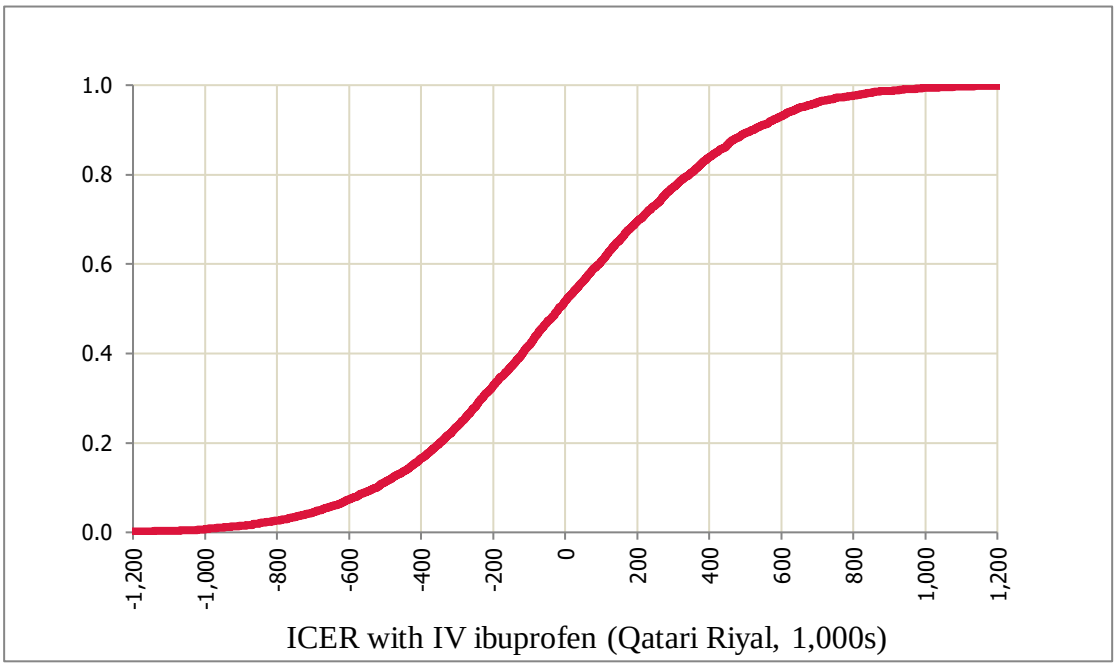

Figure 4.12. Incremental cost-effectiveness ratio (ICER, Qatari Riyal/success) acceptability curve for IV ibuprofen versus oral paracetamol

The tornado diagram of the regression coefficient rank in Figure 4.13 demonstrates that the probability of success with no AEs of oral paracetamol had the strongest correlation with the ICER, followed by the no response to the first course, with receiving a second course, for both study drugs, followed by the success with no AEs with IV ibuprofen.

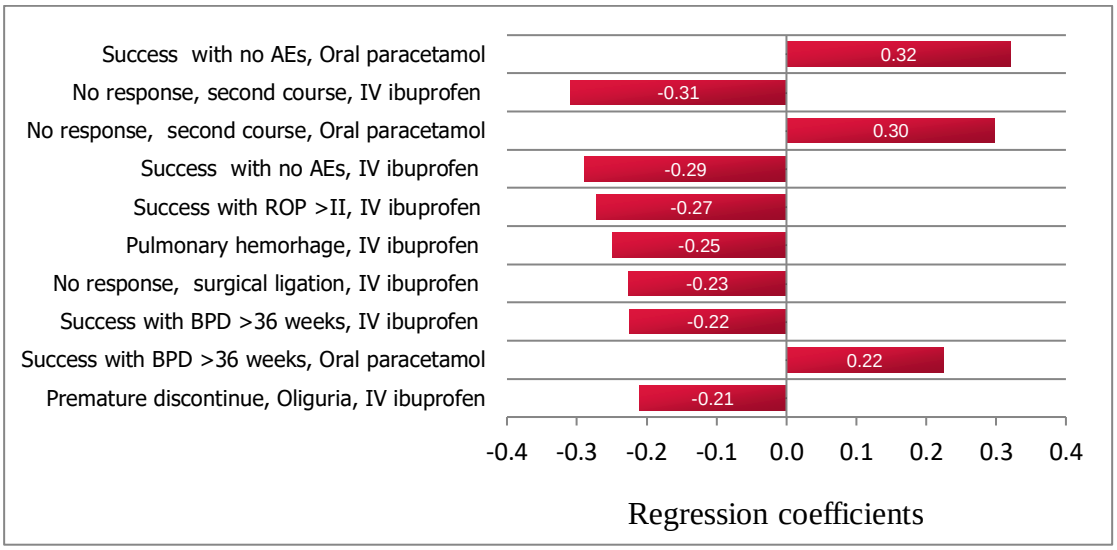

Figure 4.13. Tornado diagram of the impact of model events on incremental cost-effectiveness ratio (IV ibuprofen versus oral paracetamol model)

Sensitivity Analysis

One-way sensitivity analysis

For the variability in acquisition costs in the ibuprofen versus indomethacin model, the model inputs with their uncertainty ranges are presented in Table 4.25. The model was overall insensitive to changes in acquisition costs, not affecting the superiority of an agent over another. Changing the acquisition costs of ibuprofen (oral or IV) or the IV indomethacin only increased the superiority of IV indomethacin against IV ibuprofen from being cost-effective to becoming dominant. Similarly, for the (oral or IV) ibuprofen versus oral paracetamol model, none of the model outcomes

was affected by the changes in the acquisition costs of any of the study drugs, as can be seen in Table 4.26.

Multivariate probabilistic sensitivity analysis

The costs of AEs, their uncertainty ranges, and the consequential model outcomes can be seen in Tables 4.27 and 4.28. All the model outcomes were insensitive to any uncertainty that was associated with the cost of AEs, in addition to the base-case probability input uncertainty, except for the ICER evaluation of IV ibuprofen and IV indomethacin. Here, however, the superiority of the IV indomethacin did not change but only increased from being cost-effective to becoming dominant. Furthermore, the distribution of dominance, cost-effective, and not cost-effective states remained robust against the base-case scenario as seen in Table 4.29 (ibuprofen versus indomethacin model) and Table 4.30 (ibuprofen versus paracetamol model).

Based on the revised tornado analysis with the multivariate sensitivity analysis of the ibuprofen versus indomethacin model, the ranking of model outcomes as per the strength of their association with the ICER outputs also did not change, where the event with the most influence was the probability of success with BPD >36 weeks, Figures 4.14 and 4.15. Similarly, for the ibuprofen versus paracetamol model, the ranking of the model's outcomes as per their influence on the ICER outputs did not change because of the multivariate sensitivity analysis, as can be seen in the revised tornado diagrams of the model in Figures 4.16 and 4.17, where success with no AEs with oral paracetamol was still the most associated outcome with the ICER.

Table 4.25. Variation Range for Variables Used in One-Way Sensitivity Analysis with Outcomes of Interest (Ibuprofen versus Indomethacin Model)

Variable	Value uncertainty range (-90%, +10%)	Average cost of oral ibuprofen *	Average cost of IV indomethacin *	Average cost of IV ibuprofen *	ICER of oral ibuprofen and IV indomethacin	ICER of IV ibuprofen and IV indomethacin*
Base-case		414,761, (413,528-415,994)	436,158, (434,762-437,554)	435,794, (434,427-437,163)	Dominance for oral ibuprofen	12,546, (-54,693-79,785) with IV indomethacin
Oral ibuprofen acquisition cost	1.5, (0.15-1.65)	500,453, (499,195-501710.7)	516,743, (515, 336-518,150)	517,418, (516,007- 518, 829)	Dominance for oral ibuprofen	Dominance for IV indomethacin
IV indomethacin acquisition cost	2,220, (222-2,442)	500, 804, (499,549-502,059)	514,986, (513,597-516,375)	517, 456, (516,047-518,866)	Dominance for oral ibuprofen	Dominance for IV indomethacin
IV ibuprofen acquisition cost	553, (55-608)	499, 934, (498, 680-501,188)	516,802, (515,410-518,194)	517,488, (516,113-518,863)	Dominance for oral ibuprofen	Dominance for IV indomethacin
Oral paracetamol acquisition cost	2.79, (0.28-3.1)	500,535, (499,312-501,758)	517,132, (515,724-518,540)	516,587, (515,206-517,968)	Dominance for oral ibuprofen	18,795, (-49,754-87,344)

ICER: incremental cost-effectiveness ratio (Qatari riyal, 95% confidence interval)*

Table 4.26. Variation Range For Variables Used In One-Way Sensitivity Analysis With Outcomes Of Interest (Ibuprofen Versus Paracetamol Model)

	Value, uncertainty range (-90%, +10%)	Average cost of oral ibuprofen *	Average cost of oral paracetamol *	Average cost of IV ibuprofen*	ICER of oral ibuprofen and oral paracetamol	ICER of IV ibuprofen and oral paracetamol
Base-case		404,970 (393,834- 416,106)	397,798 (386,363- 409,233)	415,588 (403,174- 428,002)	Dominance for oral paracetamol	Dominance for oral paracetamol
Oral ibuprofen acquisition cost	1.5, (0.15-1.65)	507,472 (506,277-508,667)	489,161 (487,921- 490,400)	490,659 (489,321- 491,997)	Dominance for oral paracetamol	Dominance for oral paracetamol
IV indomethacin acquisition cost	2,220, (442-222, 2)	507,495 (506,322- 508,668)	419,396 (490,167- 492,625)	488,975 (487,639- 490,311)	Dominance for oral paracetamol	Dominance for oral paracetamol
IV ibuprofen acquisition cost	553, (55-608)	508,042 (506,858- 509,225)	488,762 (487,531- 489,993)	489,032 (487692- 490372)	Dominance for oral paracetamol	Dominance for oral paracetamol
Oral paracetamol acquisition cost	2.79, (0.28-3.1)	507,481 (506,287- 508,675)	489,474 (515,724- 518,540)	491,064 (489,719- 492,409)	Dominance for oral paracetamol	Dominance for oral paracetamol

ICER: incremental cost-effectiveness ratio (Qatari riyal, 95% confidence interval) *

Table 4.27. Variation Range for Cost of Adverse Events (AEs) Used in Multivariate Sensitivity Analysis, and Subsequent Changes in Outcomes Of Interests (Ibuprofen Versus Indomethacin Model)

Input variable	Value, uncertainty range (±10%)	Average cost of oral ibuprofen *	Average cost of IV indomethacin *	Average cost of IV ibuprofen*	ICER of oral ibuprofen and IV indomethacin	ICER of IV ibuprofen and IV indomethacin
Base-case		414,761 (413,528-415,994)	436,158 (434,762-437,554)	435,794 (434,427-437,163)	Dominance for oral ibuprofen	QAR 12,546 (-54,693- 79,785)
Cost of events						
ROP	91,700, (82,530-100,870)	500,371 (499,102-501,640)	515,407 (514,019-516,795)	517,823 (516,433-519,213)	Dominance for oral ibuprofen	Dominance for IV indomethacin
PVL	108,980, (98,082-119,878)					
BPD	170,754, (153,679-187,829					
Pulmonary hemorrhage	90,122, (81,110-99,134)					
IVH	93,894, (84,505-103,283)					
NEC	119,274, (107,347-131,201)					
GIB	61,437, (55,293-67,581)					
Intestinal perforation	120,384, (108,346-132,422)					
Oliguria	4,532, (4079-4985)					

PVL: periventricular leukomalacia, ROP: retinopathy of prematurity, BPD: bronchopulmonary dysplasia, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, GIB: gastrointestinal bleeding
ICER: Incremental cost-effectiveness ratio (Qatari riyal, 95% confidence interval)*

Table 4.28. Variation Range for Cost of Adverse Events (AEs) used in Multivariate Sensitivity Analysis, and Subsequent Changes in Outcomes of Interest (Ibuprofen versus Paracetamol Model)

Input variable	Distribution uncertainty (±10%)	Average cost of oral ibuprofen *	Average cost of oral paracetamol *	Average cost of IV ibuprofen*	ICER of oral ibuprofen and oral paracetamol	ICER of IV ibuprofen and oral paracetamol
		404,970 (393,834-416,106)	397,798 (386,363-409,233)	415,588 (403,174-428,002)	Dominance for oral paracetamol	Dominance for oral paracetamol
Cost of events						
ROP	91,700, (82,530-100,870)	507,673 (506,479-508,867)	490,079 (488,846-491,311)	490,919 (489,592-492,246)	Dominance for oral paracetamol	Dominance for oral paracetamol
PVL	108,980, (98,082-119,878)					
BPD	170,754, (153,679-187,829					
Pulmonary hemorrhage	90,122, (81,110-99,134)					
IVH	93,894, (84,505-103,283)					
NEC	119,274, (107,347-131,201)					
GIB	61,437, (55,293-67,581)					
Intestinal perforation	120,384, (108,346-132,422)					
Oliguria	4,532, (4079-4985)					

PVL: periventricular leukomalacia, ROP: retinopathy of prematurity, BPD: bronchopulmonary dysplasia, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, GIB: gastrointestinal bleeding
ICER: Incremental cost-effectiveness ratio (Qatari riyal, 95% confidence interval) *

Table 4.29. Multivariate Sensitivity Analysis of Ibuprofen versus Indomethacin

	Dominance	Cost-effective	Not Cost-effective
Oral ibuprofen versus IV indomethacin			
Base-case	59%	33%	8%
Multi-variate analysis	59%	34%	7%
IV ibuprofen versus IV indomethacin			
Base-case	50%	9%	41%
Multi-variate analysis	51%	10%	39%

Table 4.30. Multivariate Sensitivity Analysis of Ibuprofen versus Paracetamol

	Dominance	Cost-effective	Not Cost-effective
Oral ibuprofen versus oral paracetamol			
Base-case	63%	19%	18%
Multi-variate analysis	61.6%	20%	18.4%
IV ibuprofen versus IV indomethacin			
Base-case	52%	39%	9%
Multi-variate analysis	50%	41.5%	8.5%

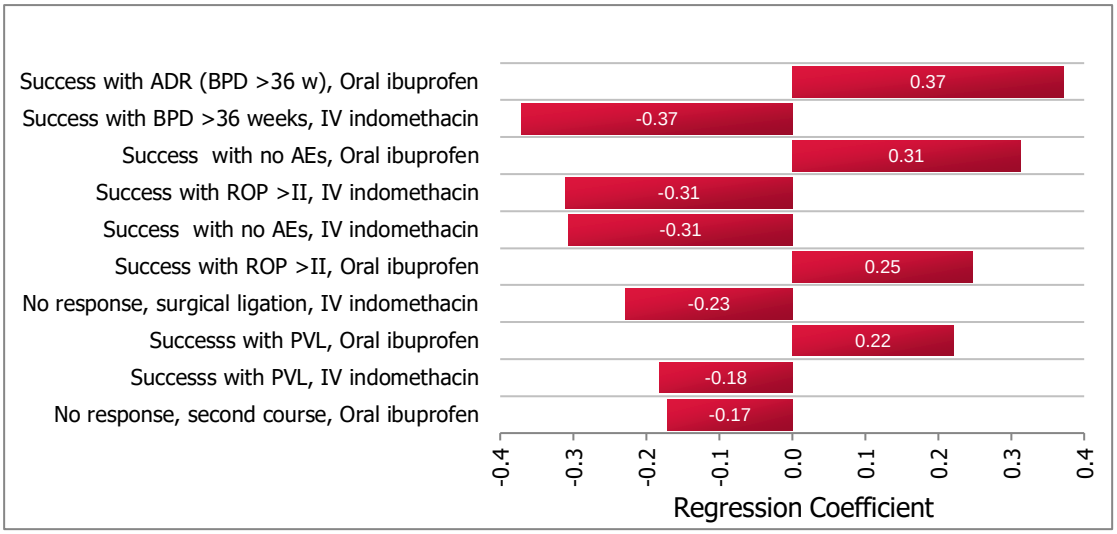

Figure 4.14. Tornado diagram of the impact of model events on incremental cost-effectiveness ratio (oral ibuprofen versus IV indomethacin model)

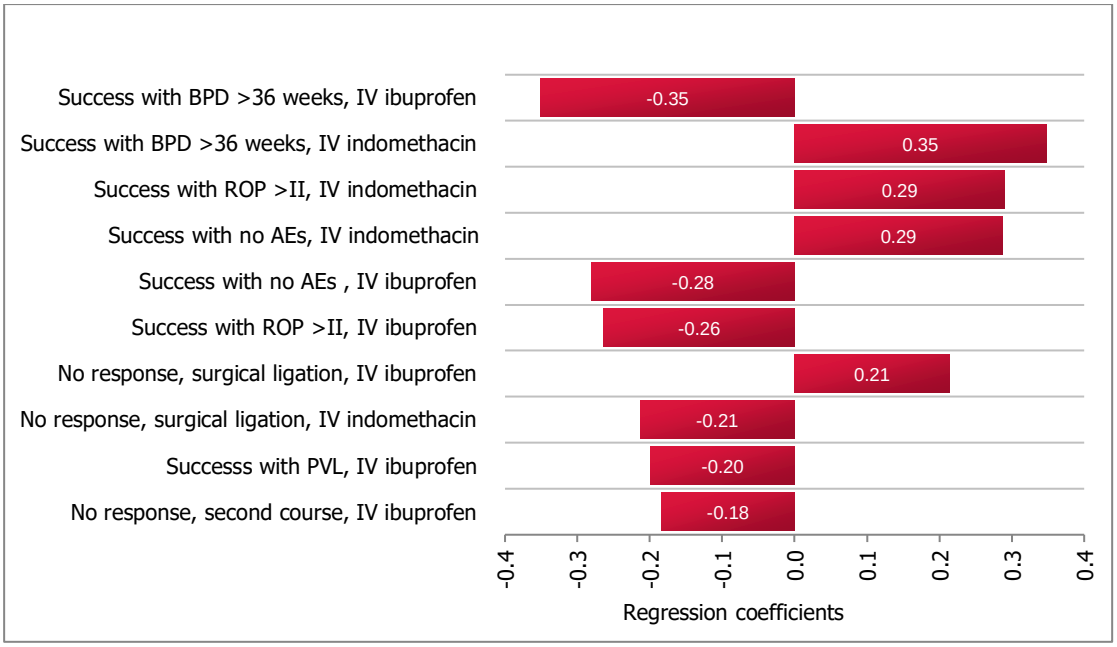

Figure 4.15. Tornado diagram of the impact of model events on incremental cost-effectiveness ratio (IV ibuprofen versus IV indomethacin model)

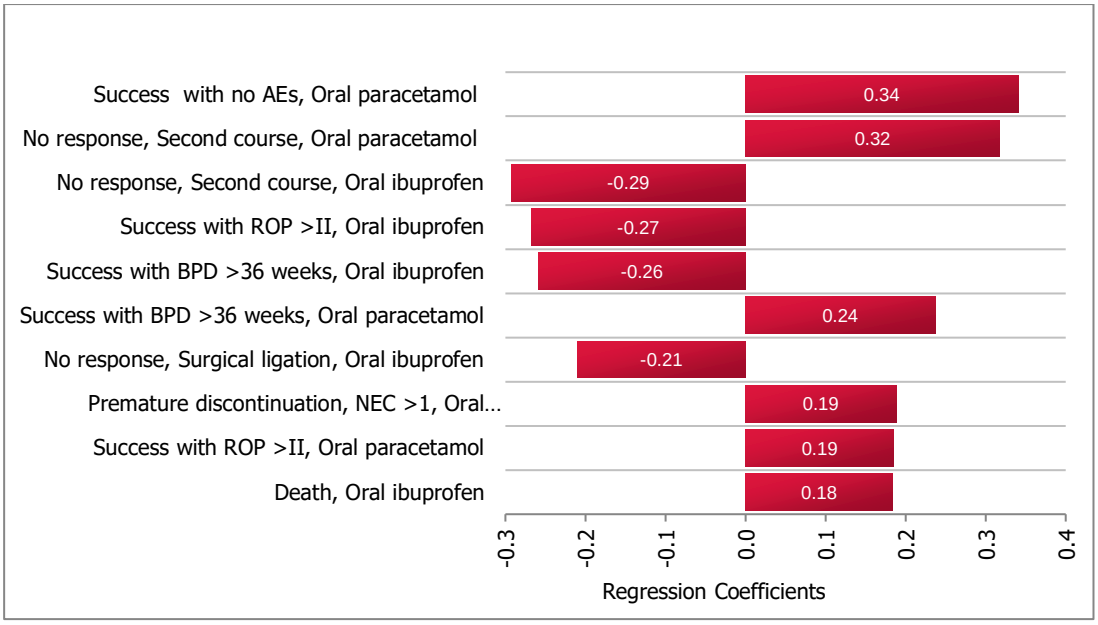

Figure 2.16. Tornado diagram of the impact of model events on incremental cost-effectiveness ratio (oral ibuprofen versus oral paracetamol model)

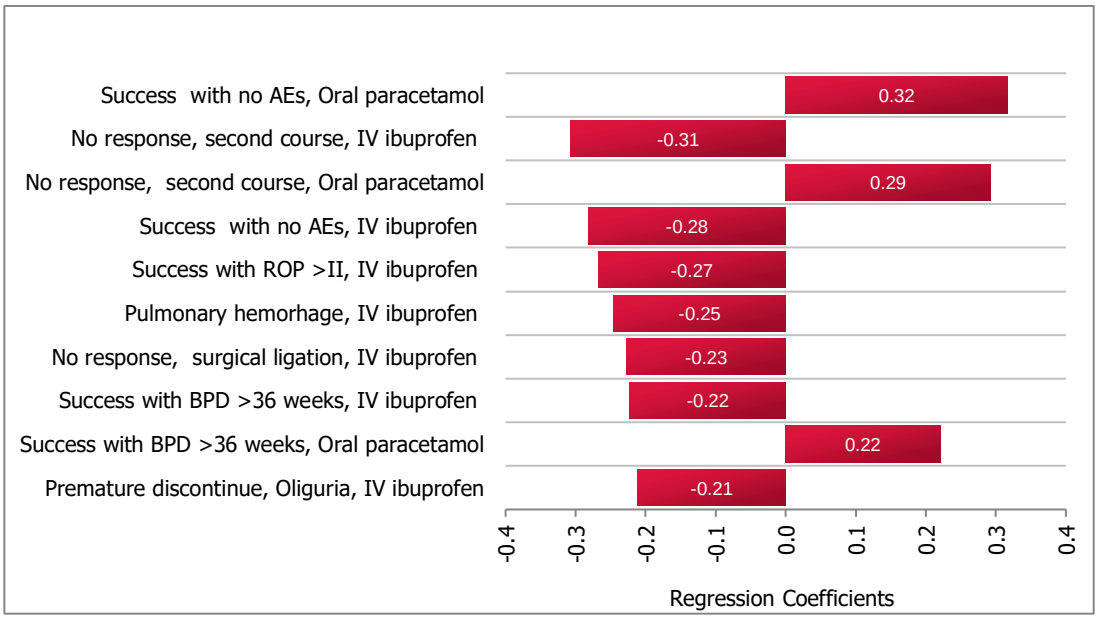

Figure 4.17. Tornado diagram of the impact of model events on incremental cost-effectiveness ratio (IV ibuprofen versus oral paracetamol model)

CHAPTER 5: DISCUSSION

Phase One: Use of Ibuprofen for the Closure of PDA in Preterm Infants in Preterm Infants. A Systematic Review of Meta-analysis

(This phase of the thesis has been derived from the following publication: Al-Shaibi S, Abushanab D, Alhersh E, Kaddoura R, Pallivalappila A, Al-Badriyeh D. Use of ibuprofen for the closure of patent ductus arteriosus in preterm infants: a systematic review of meta-analyses. Journal of Comparative Effectiveness Research. 2021;10(7):549-568.)

This systematic review of MAs summarizes the comparative evidence about the use of ibuprofen, including versus indomethacin and paracetamol, to treat PDA infants in the NICU, including different formulations. The review included seven MAs published within the last decade, including three NMAs (59, 121, 122) and two Cochrane reviews (56, 98). Included patients in all MAs were preterm infants. All MAs were based on RCTs, with two MAs, including observational studies (121, 123). The primary outcome measure in all included MAs was focusing on the closure rate of the PDA upon treatment. Successful PDA closure is generally defined as a transductal diameter of less than 1.5 mm via cardiac ECHO, by 24 hours after receiving one course of ibuprofen therapy; whereby, the commonly suggested standard ibuprofen dose is an initial dose of 10 mg/kg ibuprofen, followed by two doses of 5 mg/kg at 24-hour intervals of either formulation (102, 125-128). Within this context, HD ibuprofen's use was also evaluated in two MAs; one against indomethacin and paracetamol (59) and one against ibuprofen's standard dose (56). Here, we note that doses were not necessarily reported in all included MAs and were summarized in Table 4.5 based on how they were reported in included studies. This also applies to the HD of ibuprofen that, based on the reported

doses (Table 4.5), seems to range from 1.5 to 2 times the standard doses; 15-20 mg/kg, followed by two doses of 7.5-10 mg/kg at 24-hour intervals of either formulation.

Mixed Ibuprofen Formulations, Standard Dose

The use of mixed oral and IV of ibuprofen was assessed against mixed oral and IV formulations of indomethacin or paracetamol in several studies. The rate of PDA closure was not statistically different using ibuprofen against indomethacin (56,121). A no-difference trend was also observed against paracetamol (98,121). For the need for surgical ligation efficacy outcome, ibuprofen was compared to indomethacin and paracetamol, where no difference was measured (56, 98, 121).

Regarding adverse events, ibuprofen was inferior to indomethacin when it comes to neonatal mortality (121). Based on the same MA; however, analyzing ibuprofen versus indomethacin based on direct and indirect comparisons of RCTs and observational studies, ibuprofen did not differ in mortality from indomethacin. Against paracetamol, mortality did not differ with ibuprofen (98, 121, 97).

Against indomethacin, ibuprofen use was significantly associated with a lower incidence of NEC, IVH, oliguria, increased creatinine level, intestinal perforation, platelet count, and days on ventilator support, at high AMSTAR and low ROBIS (56). As per a low AMSTAR with unclear ROBIS NMA by Marconi et al. (121), however, the NEC advantage with ibuprofen was cancelled, as no difference in GIB was reported, and lower rates of BPD and significantly reduced serum bilirubin levels were associated with indomethacin. Compared to paracetamol, ibuprofen was not differently related to neonatal mortality, NEC, BPD, IVH, and oliguria events (121, 97). However, paracetamol was associated with a lower incidence of GIB (98, 121, 97), increased serum bilirubin (98), and decreased platelet count post-treatment (98).

IV Ibuprofen, Standard Dose

Three MAs (59, 122, 123) reported no difference between IV ibuprofen and IV indomethacin for successful PDA closure. However, against oral paracetamol, IV ibuprofen was inferior for PDA closure based on one MA, with moderate AMSTAR and low ROBIS (59), including when IV ibuprofen is via continuous infusion. Based on the SUCRA analysis by Mitra et al. (59), the IV ibuprofen had a low median rank of 8 amongst ten treatment modalities for PDA closure (Table 4.5). Regarding the need for surgical ligation, in two studies, the standard dose IV ibuprofen did not differ from the IV indomethacin (59,123).

The neonatal mortality, NEC, IVH, GIB, and intestinal perforation did not differ between IV ibuprofen and IV indomethacin based on three studies (59,122,123). This included the IV continuous infusion of ibuprofen for mortality and NEC (59). No difference in the mortality, NEC, and IVH events rates was also reported against paracetamol in one study (59), including the IV continuous infusion of ibuprofen for NEC (59). Based on the Mitra et al. SUCRA analysis (59), the IV ibuprofen ranked 6th amongst ten treatment modalities for association with NEC events (Table 4.8).

One MA reported IV ibuprofen to be inferior to IV indomethacin concerning the BPD events, with low AMSTAR and unclear ROBIS (122). However, the rate of the BPD event between IV ibuprofen and indomethacin was not found different in two other MAs, at moderate AMSTAR and low ROBIS (59) and critically low AMSTAR and high ROBIS (123), including in the case when the IV ibuprofen was a continuous infusion (59). The BPD with IV ibuprofen was also not different compared to oral paracetamol (59).

IV ibuprofen had a significantly lesser association with elevated creatinine levels and oliguria than IV indomethacin (59,123). However, oliguria was not different between IV ibuprofen and oral paracetamol (59).

Oral Ibuprofen, Standard Dose

For PDA closure, oral ibuprofen was not statistically different from IV indomethacin based on two MAs (59,123) and was also not different compared to both oral and IV indomethacin in a third study (56). Against oral paracetamol, oral ibuprofen was not different for the PDA closure in two MAs (59,97). Out of four pooled pairwise analyses that evaluated the need for surgical ligation with oral ibuprofen versus indomethacin, three reported no difference than IV indomethacin (56,59,123). In the remaining study, oral ibuprofen did not perform differently from mixed oral and IV indomethacin administration (56).

Against IV indomethacin, oral ibuprofen was not statistically different in neonatal mortality (59,122) and not significantly different in BPD (59,123). Mortality and BPD were not different between oral ibuprofen and oral paracetamol (59). Based on a SUCRA analysis (59), oral ibuprofen has the 3rd and 2nd lowest risks for mortality and BPD, respectively, among ten treatment modalities (Tables 4.7 and 4.9). IVH was not different between oral ibuprofen and IV indomethacin or oral paracetamol (59). The only GIB study with oral ibuprofen reported a not statistical difference from IV indomethacin (123). Oral ibuprofen was significantly associated with less NEC than mixed oral and IV indomethacin or IV indomethacin (56,59). In contrast, oral ibuprofen was reported as not different from IV indomethacin for NEC events in one study with critically low AMSTAR and high ROBIS (123). Oral ibuprofen was also compared against oral paracetamol with no significant difference in the incidence of NEC (59). Oliguria was statistically less with oral ibuprofen compared to IV indomethacin (59)

but was not different compared to oral paracetamol (59). Oral ibuprofen was ranked 4th in risk for oliguria among ten treatment modalities based on one SUCRA analysis (Table 4.12) (59). In one MA, oral ibuprofen was not different in creatinine levels compared to IV indomethacin, but was associated with a significantly reduced increase in creatinine levels compared to oral indomethacin (123). In another study, against mixed oral and IV formulations use of indomethacin, no difference was reported with oral ibuprofen (56).

Oral Ibuprofen versus IV Ibuprofen, Standard Dose

Only one study evaluated the effect of ibuprofen formulation on PDA closure (56); oral ibuprofen had a lower risk of failure to close the PDA than IV ibuprofen. In the same study, however, for the need for surgical ligation, no difference was observed. For adverse events, BPD and IVH were not different between the two formulations in one study (59). With a similar trend but at a higher AMSTAR, oliguria did not differ between the two formulations in another study (56). Only the serum creatinine level differed between the formulations, where oral ibuprofen was associated with a lower increase in levels (56). One MA reported the need for retreatment with oral versus IV ibuprofen to close the PDA, which was statistically significant with oral ibuprofen (59). Other efficacy and safety outcomes were not different between the oral and IV formulations.

High Dose Ibuprofen, Oral and IV Formulations

One MA, by Mitra et al., reported the difference between HD ibuprofen and IV indomethacin (59), where HD oral ibuprofen was associated with a significant advantage in relation to PDA closure and the need for surgical ligation. Still, it was not different with neonatal mortality, NEC, and BPD. HD IV ibuprofen performed differently from HD oral ibuprofen against IV indomethacin, where there was no

difference for both PDA closure and the need for surgical ligation. HD IV ibuprofen was not different from IV indomethacin concerning neonatal mortality, NEC, BPD, IVH, and oliguria (59).

According to Mitra et al., HD oral and IV ibuprofen performed similarly against oral paracetamol (59). No difference with HD ibuprofen against the oral paracetamol was observed for PDA closure and the need for surgical ligation. A similar trend was observed for neonatal mortality and NEC.

Regarding the effect with HD versus standard dose of mixed oral and IV ibuprofen use, by Ohlsson et al. (56), PDA closure was significantly better achieved when at HD, but not for the need for surgical ligation, based on one RCT. A similar trend of no difference was observed with oliguria and creatinine levels, based on one RCT (56).

Looking at the ibuprofen formulations separately, one MA found no difference between HD oral ibuprofen versus standard-dose oral ibuprofen for PDA closure (59) but reported that HD of either oral or IV ibuprofen was more effective than standard-dose IV ibuprofen for PDA closure. For the need for surgery, this was significantly lesser with HD oral ibuprofen than standard doses of either oral or IV ibuprofen (59). In contrast, the HD IV ibuprofen did not perform differently for the same outcome from the standard doses of either oral or IV ibuprofen (59). Based on the same MA, HD IV ibuprofen did not perform differently from either oral or IV ibuprofen for BPD and IVH events. This is consistent with the SUCRA analysis performed by Mitra et al. in their NMA [(59); whereby, for PDA closure, out of nine treatment modalities, the two highest-ranked were HD oral ibuprofen and HD IV ibuprofen. Based on the 95% CI reported, no significant difference could be seen within at least the first five ranked treatments, including oral ibuprofen and oral paracetamol (Table 4.5).

In the current study, general observations are consistent with recent trends of having ibuprofen as first-line therapy for PDA in neonates, particularly against the older and previous standard treatment, indomethacin, due to reported enhanced efficacy and reduced toxicity in the literature (116, 129-132). Paracetamol is a more recently suggested alternative for PDA, where it demonstrated efficacy and safety, particularly advantageous in patients with clinical contraindications to ibuprofen (116). Our observation is that paracetamol, overall, performed better than indomethacin compared to ibuprofen. Also consistent with our observations is the recent trends of increased interest in the off-label oral ibuprofen compared to IV ibuprofen, particularly as IV ibuprofen may not be available in all practices, especially in low-income countries. Oral ibuprofen has the advantage of a lower acquisition cost compared to IV ibuprofen, added to ease of availability and administration (133-139).

The current study's applicability is limited by the lack of information about a consistent administration timing of ibuprofen medication. The medication timing highly depends on the clinical diagnostic criteria used to define the hsPDA. However, a study by Koehne et al. found that it is normal for hsPDA to be clinically silent for the first two to three days of life and, hence, accurate and early diagnosis of hsPDA best depends on early echocardiographic assessment (140). There is, nonetheless, no evidence in included MAs of overall consistency in how early and how often the echocardiography was performed for PDA diagnosis in individual studies. In the Cochrane review, by Ohlsson et al. (56), for example, the diagnosis among included RCTs varied from prophylactic (within 24 hours) to 2, 3, 7, or 21 days of life, to selective, to not stated.

Several limitations exist in the current systematic review. The analysis only included outcomes reported in two or more MAs. Hence, this did not include all

reported efficacy and safety outcomes in the literature, excluding, for example, neurodevelopment impairment. This does not undermine how important such outcomes are. However, given the objective of the current review, which is to simplify access to summaries of outcomes where an information overload exists, a decision was made whereby outcomes that are reported in only one MA are easily accessible and interpretable, noting that, for the interest of care providers, we identified the literature studies were these were reported (Table 4.18). Besides, some studies were included in more than one included MAs, which may create double-counting of data, which is inherent in systematic reviews of MAs and is challenging to eliminate. However, as already discussed, we looked to minimize this limitation's impact by excluding older versions of more recent MAs' updates. The language-restricted search is another limitation and might have missed relevant non-English published studies. No resources were available to authors, however, to translate non-English studies if found. Furthermore, while we believe that our literature search was comprehensive and included all relevant studies, it is always possible that additional search terms and combinations of them may identify other studies.

Phase Two: Cost-effectiveness of Ibuprofen versus Indomethacin or Paracetamol for the Treatment of PDA in Preterm Neonates

Internationally, the optimal medication for PDA in NICUs is highly controversial and remains unclear as there are no universal guidelines or consensus regarding the most appropriate treatment approach, including the dosage form. The uncertainty surrounding the relative variability in the effectiveness and safety performance of the different study drugs is further amplified when also considering the relative economic impact. In the medical literature, to date, there is no clear,

comprehensive evidence that includes the economic impact for guiding the comparative drugs for PDA, including in Qatar.

Therefore, the objective of the second phase of this thesis was to conduct a first-time pharmacoeconomic evaluation to compare between ibuprofen and each of indomethacin and paracetamol as first-line for the closure of PDA in premature neonates. To compare between the oral and IV ibuprofen formulations or between indomethacin and paracetamol is outside the scope of the current research. The interest is only in examining indomethacin and paracetamol as potential alternatives to the ibuprofen currently used in HMC.

Indomethacin and ibuprofen are the two COX inhibitors approved by the US FDA for the closure of ductus in premature babies. Apart from efficacy and safety, the choice of one drug over the other is also influenced by the availability of both drugs and the IV or enteral preparation in the local area. Although the use of paracetamol to close a hsPDA has increased in recent years, it is still considered off-label. There is no commercially available indomethacin oral formulation for use in infants. In studies where indomethacin was administered orally, the authors prepared a saline–dextrose solution or water suspension of the drug powder from capsules (141). As for paracetamol, all formulations were oral in the RCTs reported in the Cochrane systematic review conducted in 2020, except for one RCT that reported IV paracetamol (98).

Compared to IV indomethacin, the base-case results of the respective model illustrated an increased probability of success, by 0.1488 (0.1704, 0.1198), in favor of oral ibuprofen. For the cost difference, this was over QAR 21,000 in favor of the oral ibuprofen. While the proportional cost associated with the success outcomes was higher with oral ibuprofen (QAR 46,686), this is overtaken by an over QAR 68,000

proportional costs in favor of the oral ibuprofen associated with the failure. Taking cost into consideration, the oral ibuprofen was dominant in 59% and cost-effective in 33% of the simulated model cases.

Compared to IV ibuprofen, however, the difference in the probability of success at base-case was 0.029 in favor of IV indomethacin. For the cost difference, this was minimal, over QAR 300 in favor of the IV ibuprofen. While the proportional cost associated with the success outcomes was higher with IV indomethacin (QAR 14,213), this was almost balanced by over QAR13,000 proportional costs in favor of the IV indomethacin associated with the failure. The IV indomethacin was dominant in 50% of the cases and, based on the WTP threshold in this study, cost-effective in only 9% of the cases with an average ICER of QAR 12,546 per additional case of PDA closure. However, IV indomethacin was not cost-effective in 41% of the cases. The superiority of IV indomethacin over IV ibuprofen, but not oral ibuprofen, is further confirmed via improved effectiveness and reduced cost with oral ibuprofen over IV oral ibuprofen as reported by Abushanab et al. in their local cohort-based study (67). Oral ibuprofen had a higher success rate for PDA closure by 27% with a lower cost, dominating IV ibuprofen in 72% of the patient cases with a mean saving of QAR 48,751 (95% CI 47,500-50,000) (67).

Regarding the comparison between oral paracetamol and ibuprofen, the mean difference in the success of PDA closure was a minimal 0.0069 in favor of oral paracetamol compared to oral ibuprofen. For the cost difference, this was over QAR 7,000 in favor of the oral paracetamol. The proportional cost associated with the success and failure outcomes was higher with oral ibuprofen by QAR 4,317 and QAR 2,855, respectively. Taking cost into consideration, oral paracetamol was 82% between dominant and cost-effective.

Also, compared to IV ibuprofen, the mean difference in the success of PDA closure was in favor of oral paracetamol, by 0.1621. For the cost difference, this was over than QAR 17,000 in favor of the oral paracetamol. While the proportional cost associated with the success outcome was higher with oral paracetamol (QAR 49,471), this is overtaken by an over QAR 67,000 proportional costs in favor of the oral paracetamol associated with the failure. Oral paracetamol was dominant over IV ibuprofen in 52% of the cases and was considered cost-effective in 39% of the cases. There are no other comparative economic values among ibuprofen, indomethacin, and paracetamol in the literature to contrast any of the above results against, but the one-way and multivariate sensitivity analyses conducted as part of all evaluations confirmed our results of favoring oral ibuprofen over IV indomethacin, IV indomethacin over IV ibuprofen, and oral paracetamol over both oral and IV ibuprofen over a range of variabilities in cost inputs and event probabilities.

Further establishing the importance of looking at secondary costs of therapies, in addition to their acquisition costs, is our breakdown analysis of the cost components of the study regimens, which, as anticipated, indicated that over 85% of the cost per patient with any of the study drugs in either model is hospitalization costs, followed by monitoring costs.

Based on the base-case tornado regression findings for both evaluations between ibuprofen versus IV indomethacin, the most influential model input on the study outcome was the likelihood of success with BPD >36 weeks with either ibuprofen or indomethacin. This is not unanticipated given that the health state of success with BPD >36 weeks did not only have the higher cost per event to it but was associated with the highest event probability in the model, just second to the outcome of success with no AEs.

For the ibuprofen versus oral paracetamol comparative model, the base-case tornado regression analysis demonstrated that the most influential model event on the study outcome was the likelihood of success with no AEs with oral paracetamol against either oral or IV ibuprofen. While the health state of success with no AEs is not associated with the highest cost per patient, it had the highest outcome probability in the model, adding to a proportional cost that contributes to the patient cost the most.

Apart from being the first pharmacoeconomic study, nationally and internationally, to evaluate the cost-effectiveness among all main pharmacotherapeutic options available for the closure of PDA in premature neonates, the study is unique in how comprehensive the decision-analytic model is. The model represents all the possible consequences of using a study drug for PDA, including discontinuation due to AEs, failure of treatment, surgical pathway, death, and the AEs that do not constitute failure and, hence, an overall cost of resource utilization is more accurately represented. Also, a strength is that the current comparative model was able to simulate a follow up of patients until discharge from the NICU at 34 weeks, as per HMC practices.

The model was populated with data to a different extent from different sources available in the literature, which was to account for missing data in each of the individual sources. The sources of clinical inputs used in our model are considered another strength in the study as they constituted the most recent (2020), highest quality Cochrane MAs, including large sample sizes of RCT patients (56, 98). Here, it is important that the inclusion criteria of the patients in the MAs are consistent with the PDA population receiving the study drugs in the local HMC setting. In addition, the success of the PDA closure study outcome is also consistent with what decision-

makers look to follow-up in PDA infants in HMC. Moreover, the regiment of study medications given to neonates for PDA treatment is identical to that routinely provided in the NICU of HMC.

There is no approved WTP cost-effectiveness threshold in Qatar. While the WHO suggests using 1-3 times the GDP per capita as the value of the threshold in a country, it is acknowledged that this is arbitrary and not based on any methodological justification (142). In addition, the average 2019 GDP per capita (PPP) in Qatar was approximately USD 94,028 (143), one of the world's highest. Thus, adopting the WHO recommendation for calculating the WTP will result in a range of values that is too wide to be directly useful, i.e., USD 64,781-194,343. In this study, we adopt a threshold value of USD 150,000, which is increasingly accepted as a higher threshold value in the literature, which is also within the range suggested by WHO for Qatar (144).

While relying on a pooled analysis of well-established RCTs comes with strong internal validity due to randomization, blindness, and control of confounding variables in the RCTs (145), the use of MAs as a source of data comes with considerable limitation to the economic assessment in this research. The MAs jeopardized the generalizability of results to the local setting due to the enrichment in included RCTs and the differences in patient demographic characteristics (145); whereby, none of the MA studies included Qatari-based research as an example. As a consequence, there can be inherent uncertainties associated with the clinical input, and it is for this reason that the decision-analytic model was based on multivariate uncertainty analysis of probability inputs at its base-case. This is an innovative approach and, to the best of our knowledge, has not been reported in the literature. This is thought to be a more meaningful and reliable representation of the outcomes,

whereby the base-case was based on a hypothetical cohort of 5,000 neonates instead of a single case, with uncertainties in a variety of input values randomly interacting, as in real-life situations. To further account for the uncertainty about generalizability, additional uncertainty was added to analyzing the model via the one-way and multivariate sensitivity analyses, which confirmed robustness.

To emphasize, however, despite robustness against uncertainty, the results of this analysis are specific to the Qatari setting, and the results of this study should not be easily extrapolated to patients in different settings, especially due to variations in resource utilization.

Although the findings of the current study are comprehensive and robust, they can only be completely validated by a follow-up future local studies that assess, retrospectively or prospectively, the comparative clinical and economic impacts of ibuprofen versus indomethacin or paracetamol in premature neonates with PDA in the Qatari HMC setting. However, this is currently difficult, mostly due to the relatively low/lacking number of patients who have received indomethacin and paracetamol as first-lines for PDA. Therefore, locally specific simulation studies, such as the current one, are considered fundamental for decision-making in local practices.

CHAPTER 6: CONCLUSION

IV ibuprofen is currently the first-line therapy for the management of PDA in Qatar, with an increasing interest in the oral dosage form of the ibuprofen as an alternative. The literature MAs indicate via high quantity and quality of evidence that ibuprofen is efficacious and safe to administer for the closure of PDA. Within the context of other available potential first-line options, however, this has not been based on any local evidence, including the economic aspect. Here, owing to contrasting quality and risk of bias, robust conclusions in relation to the comparative effectiveness and safety of ibuprofen against indomethacin or paracetamol cannot be obtained from all relevant MAs. From the HMC perspective in Qatar, the core objective of the current thesis was to follow the use of the ibuprofen versus indomethacin or paracetamol in a simulated cohort of PDA patients, relying on the data from the best available sources of evidence in the literature and looking at the main clinical and economic consequences of the study drugs as per a realistic follow up duration until discharge.

Taking into consideration the assumptions and limitations made in our research, the results seem to favor oral paracetamol as the superior alternative first-line therapy to ibuprofen for PDA in Qatar. Oral paracetamol was between cost-effective and dominant over both oral and IV ibuprofen formulations. Next to oral paracetamol, oral ibuprofen is favorable. The latter was also between cost-effective and dominant against indomethacin as a potential first-line alternative to the IV ibuprofen for PDA. The same was not true for the IV ibuprofen, which was dominated by IV indomethacin as a proposed alternative.

From the perspective of HMC, results are in contrast to HMC practices in relation to two aspects. First, while IV ibuprofen is currently the first-line of therapy for the

treatment of PDA, IV indomethacin, similar to oral ibuprofen, are potentially superior alternatives, noting the availability of both oral ibuprofen and IV indomethacin in the formulary of HMC. Second, oral paracetamol has only been used so far in HMC on an arbitrary basis, based on personal experiences and opinions. However, this is a practice that may need to change; whereby, adopting oral paracetamol as a solid alternative to ibuprofen might be ideal for the NICU in HMC.

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APPENDIX A: PRISMA CHECKLIST TOOL

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	37
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	37
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	37
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	39
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	40
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	39
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	158
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	40
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	40
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	41
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	40
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency for each meta-analysis.	41

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	41
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	56
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	59-61
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	89-90
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	66-88
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	89-90
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	129
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	135-136
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	129-135
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

APPENDIX B: LITERATURE SEARCH STRATEGIES

PubMed search strategy

Search No.#	Query	Result
1	"Ductus Arteriosus, Patent"[Mesh]	
2	PDA	
3	“persistent arterial duct”	
4	**#1 OR #2 OR #3**	**17462**
5	"Ibuprofen"[Mesh]	
6	"Anti-Inflammatory Agents, Non-Steroidal"[Mesh]	
7	**#4 AND (#5 OR #6)**	**596**
8	**#7 AND ([meta-Analysis]/lim OR [review]/lim OR [systematic review]/lim)**	**126**
9	**#8 AND [humans]/lim**	**116**

Embase search strategy

Search No.#	Query	Result
1	'nonsteroid antiinflammatory agent'/exp	
2	'ibuprofen'/exp	
3	**#1 OR #2**	**742005**
4	'patent ductus arteriosus'/exp	
5	'patent arterial duct'/exp	
6	'persistent arterial duct'/exp	
7	'persistent ductus arteriosus'/exp	
8	**#3 AND (#4 OR #5 OR #6 OR #7)**	**2067**
9	**#8 AND [english]/lim**	**1891**
10	**#9 AND [embase]/lim**	**1779**

Cochrane CENTRAL search strategy

Search No.#	Query	Result
1	**'patent ductus arteriosus' OR 'persistent arterial duct' OR 'persistent ductus arteriosus' OR 'patent arterial duct' OR 'PDA'**	**245**
2	**#1 in Title Abstract Keyword**	**55**
3	**#2 AND ('ibuprofen' OR 'nonsteroid antiinflammatory agent') - (Word variations have been searched)**	**17**

APPENDIX C: ETHICS EXEMPTION

Qatar University Institutional Review Board **QU-IRB**
QU-IRB Registration: IRB-QU-2020-006, QU-IRB, Assurance: IRB-A-QU-2019-0009

January 20, 2021

Dr. Daoud Al-Badriyeh
College of Pharmacy
Qatar University
Phone: 4403 5591
Email: daoud.a@qu.edu.qa

Dear Dr. Daoud Al-Badriyeh,

Sub.: Determination of Non-human Subject Research
Ref.: Student, Samaher AL-Shaibi, e-mail: sa1306774@student.qu.edu.qa
Project Title: "Cost-effectiveness analysis (CEA) of ibuprofen versus indomethacin or acetaminophen (paracetamol) for the treatment of patent ductus arteriosus (PDA) in preterm neonates in Qatar"

Thank you for the submission of your application materials for the above-named project. Your application and supporting documents submitted have been examined by the QU-IRB. The QU-IRB has determined this project does not meet the definition of human subject research under the purview of the IRB according to MOPH and QU regulations.

The QU-IRB understood that the project aimed to anticipate the economic advantages among the different available options for PDA from the HMC perspective, to guide practices for when the three agents are available for utilization in the neonatal setting of HMC for PDA. Therefore, a simulation-based decision-analytic model will be constructed that is primarily based on clinical data obtained only from published literature data.

Based on the purpose above and the nature of the study (documents examined by an IRB member), QU-IRB hereby makes the determination that this is classified as non-human subject and does not require IRB review and approval. We will retain a copy of this correspondence within our records.

However, the applicant needs to comply with regulations governing such studies at QU, which may potentially include approval from relevant unit/section head and data sharing agreement.

Your project determination number is: QU-IRB 007-NR/21. Please include your project title and reference number in all correspondence with this committee.

Best wishes,

Dr. Mohamed Errara
Vice Chair, QU-IRB

Institutional Review Board
(IRB)
Office Of Academic Research

APPENDIX D: PROBABILITY OF EVENTS

Clinical probability	Oral ibuprofen	IV indomethacin	IV ibuprofen
Success (PDA closure)	0.9034	0.7546	0.7256
Success with AE	0.4049	0.5347	0.5308
o **ROP >II**	0.2799	0.4547	0.3619
o **PVL**	0.1895	0.1079	0.1446
o **BPD >36 W**	0.5306	0.4374	0.4936
Success without AE	0.5951	0.4653	0.4692
Failure	0.0966	0.2454	0.2744
Failed to close	0.0162	0.0669	0.0965
o **Retreatment**	0.6771	0.5803	0.6599
o **Surgical ligation**	0.3229	0.4197	0.3401
Death	0.0156	0.0347	0.0424
Premature discontinuation	0.0649	0.1438	0.1356
o **Pulmonary hemorrhage**	0.0207	0.1003	0.1602
o **IVH**	0.2638	0.1657	0.2645
o **NEC >1**	0.1049	0.1288	0.1319
o **GIB**	0.5562	0.1844	0.2081
o **intestinal perforation**	0.0425	0.1830	0.1436
o **Oliguria <1**	0.0119	0.2378	0.0916

Clinical probability	Oral ibuprofen	Oral paracetamol	IV ibuprofen
Success (PDA closure)	0.6258	0.6327	0.4706
Success with AE	0.2972	0.1911	0.4250
o **ROP >II**	0.5234	0.3500	0.6204
o **PVL**	0.1758	0.2733	0.1229
o **BPD >36 W**	0.3009	0.3767	0.2566
Success without AE	0.7028	0.8089	0.5750
Failure	0.3742	0.3673	0.5294
Failed to close	0.1625	0.1810	0.2133
o **Retreatment**	0.8644	0.9230	0.8551
o **Surgical ligation**	0.1356	0.0770	0.1449
Death	0.0663	0.0726	0.0398
Premature discontinuation	0.1455	0.1138	0.2762
o **pulmonary hemorrhage**	0.2154	0.2863	0.4041
o **IVH**	0.1085	0.1582	0.0264
o **NEC >1**	0.1605	0.2560	0.0490
o **GIB**	0.2423	0.1254	0.0220
o **intestinal perforation**	0.0137	0.0000	0.0112
o **Oliguria <1**	0.2596	0.1741	0.4871