



BeNeDuctus Trial

Multi-center, randomized non-inferiority trial of early treatment versus expectative management of patent ductus arteriosus in preterm infants

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Dutch Working Group on Neonatal Haemodynamics

Contact Details

Willem P. de Boode, MD PhD
Radboudumc Amalia Children's Hospital
Department of Pediatrics, Division of Neonatology
Internal postal code 804
Geert Grooteplein Zuid 10
6525 GA Nijmegen
The Netherlands

Phone +31 24 3614430
Mobile +31 6 21198028
Fax +31 24 3616428
Email willem.deboode@radboudumc.nl
Info beneductus.kg@radboudumc.nl
Web <http://neonatalogynetwork.eu/studies/beneductus>

Amalia Children's Hospital
Radboudumc

PROTOCOL TITLE

Multi-center, randomized non-inferiority trial of early treatment versus expectative management of patent ductus arteriosus in preterm infants

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Project leader	W.P. de Boode, MD PhD Radboudumc Amalia Children's Hospital Department of Pediatrics, Division of Neonatology (804) Geert Grooteplein Zuid 10, 6525 GA Nijmegen, The Netherlands Phone: +31 24 3614430; Email: willem.deboode@radboudumc.nl
Study Sites	<u>Sites (names and contact details principal investigators in appendix § XI.1.):</u> Neonatal Intensive Care Unit (NICU) Radboudumc Nijmegen (RUMC) NICU University Medical Center Groningen (UMCG) NICU Academic Medical Center Amsterdam (AMC) NICU Maastricht University Medical Center (MUMC) NICU Erasmus Medical Center Rotterdam (EMCR) NICU Vrije Universiteit Medical Center Amsterdam (VUMC) NICU Leiden University Medical Center (LUMC) NICU University Medical Center Utrecht (UMCU) NICU Isala Kliniek Zwolle (IKZ) NICU Maxima Medical Center Veldhoven (MMC) NICU Erasme Hôpital Cliniques Universitaires de Bruxelles (HEB) NICU Universitair Ziekenhuis Brussel (UZB) NICU Universitair Ziekenhuis Antwerpen (UZA) NICU Universitair Ziekenhuis Leuven Gasthuisberg (UZL)
Sponsor	Radboudumc Amalia Children's Hospital Geert Grooteplein Zuid 10, 6525 GA Nijmegen, The Netherlands
Subsidising Party	The Netherlands Organization for Health Research and Development (ZonMw); project number 843002622
Independent Physician	M. Schreuder, MD PhD Radboudumc Amalia Children's Hospital Department of Pediatrics, Division of Pediatric Nephrology (804) Geert Grooteplein Zuid 10, 6525 GA Nijmegen, The Netherlands Phone: +31 24 3614430; Email: michiel.schreuder@radboudumc.nl

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Head of Department of Pediatrics Prof.dr. C. Noordam, MD PhD Radboudumc Amalia Children's Hospital		
Project Leader/Principal Investigator W.P. de Boode, MD PhD Department of Neonatology Radboudumc Amalia Children's Hospital		

List of abbreviations and relevant definitions

AGA	Appropriate for Gestational Age
BIA	Budget Impact Analysis
BNP	B-type Natriuretic Peptide
BPD	BronchoPulmonary Dysplasia
BSID-III-NL	Bayley Scales of Infant and Toddler Development, Third Dutch Edition
CBCL	Child Behavior Check List
CEA	Cost Effectiveness Analysis
COX	Cyclooxygenase
COXi	Cyclooxygenase inhibition/inhibitor(s)
CRF	Case Report Form
cTnT	Cardiac troponin T
CUS	Cerebral ultrasound
DAo	Descending aorta
DOL	Day of life
dPDA	Diameter of patent ductus arteriosus
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
E/D	Echocardiography/Doppler
EDF _{PDA}	End-diastolic flow patent ductus arteriosus
GA	Gestational age
GCP	Good Clinical Practice
hsPDA	Haemodynamically significant patent ductus arteriosus
IBU	Ibuprofen
ICH	Intracranial haemorrhage
INDO	Indomethacin
IUGR	Intrauterine growth retardation
IVH	Intraventricular haemorrhage
LA/Ao-ratio	Left atrial to aortic ratio
LPA	Left pulmonary artery
LVO	Left ventricular output
Movement ABC 2-NL	Movement Assessment Battery for Children, Second Dutch Edition
NEC	Necrotising enterocolitis
NT-proBNP	Amino-terminal B-type natriuretic peptide
P/IVH	Peri-/intraventricular haemorrhage

PBF	Pulmonary blood flow
PCA	Pericallosal artery
PDA	Patent ductus arteriosus
PEEP	Positive end-expiratory pressure
PFO	Patent foramen ovale
PH	Pulmonary haemorrhage
PI	Principle investigator
PMA	Postmenstrual age
PNA	Postnatal age
PPHN	Persistent pulmonary hypertension of the newborn
PVE	Periventricular echogenicity
PVL	Periventricular leukomalacia
Qp	Pulmonary blood flow
Qp/Qs-ratio	Ratio of pulmonary to systemic blood flow
Qs	Systemic blood flow
R/F-ratio	Reversed to forward flow ratio
RCT	Randomized controlled trial
ROP	Retinopathy of prematurity
Rp/Rs index	Ratio of the pulsatility index of the LPA to the pulsatility index of the DAo
SBF	Systemic blood flow
SGA	Small for gestational age
SIP	Spontaneous intestinal perforation
SMA	Superior mesenteric artery
SVC	Superior vena cava
TC	Celiac trunk
TRF	Teacher Report Form

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SUMMARY

Background: Much controversy exists about the optimal management of a patent ductus arteriosus (PDA) in preterm infants, especially in those born at a gestational age < 28 weeks or with a birth weight ≤ 1000 grams. A common understanding is that the actual approach with medical or surgical treatment of a PDA seems not to reduce the risk of major neonatal morbidities. This might be related to the fact that a substantial portion of preterm infants are probably treated unnecessarily, because the PDA might have closed spontaneously without specific interventions. This would imply over-treatment with an increase in iatrogenic risk of adverse effects related to the used drugs and/or surgical ligation. An expectative approach is gaining interest, although convincing evidence is still lacking.

Objective: To investigate whether in preterm infants, born at a GA less than 28 completed weeks, with a PDA an expectative management is not inferior to early treatment with regard to the composite of mortality and/or NEC and/or BPD at a PMA of 36 weeks.

Study design: Multicenter, randomized, non-inferiority study conducted in neonatal intensive care units (NICU's) in the Netherlands and Belgium.

Study population: Preterm infants (GA<28 weeks) with an echocardiographic confirmed PDA with a transductal diameter >1.5 mm.

Intervention: Expectative PDA management is characterized as 'watchful waiting'. No intervention is initiated with the intention to close a PDA.

Usual care: The preterm infants with a PDA are treated with COX-inhibition by Ibuprofen.

Outcome parameters: The primary outcome is the composite of mortality, and/or NEC (Bell stage ≥ IIa), and/or BPD, defined as the need for supplemental oxygen need, all at a postmenstrual age of 36 completed weeks. Secondary outcome parameters are short term sequelae of cardiovascular failure, adverse effects during the stay in the hospital and long-term neurodevelopmental consequences assessed at an corrected age of 2 years. Consequences regarding health economics are evaluated by cost effectiveness analysis and budget impact analysis.

Burden and risks associated with participation, benefit and group relatedness: All patients in this study are treated according current (inter)national guidelines and local protocols regarding neonatal intensive care management. The administration of ibuprofen or Indomethacin does not pose an extra burden on the patient and is considered routine treatment in preterm infants with a PDA in a majority of neonatal intensive care centers. No extra investigations or interventions are needed in this study. Patients that aren't treated with COXi are refrained from potential side effects of this drug.

A restrictive approach towards a PDA is increasingly used in many centers worldwide without an concomitant increase in mortality or morbidity related to a PDA. No causal relationship has been proven between a (hemodynamically significant) PDA and the risk of conditions related to pulmonary hyperperfusion (f.e BPD and PH) and/or systemic hypoperfusion (f.e NEC, renal failure and PVL). Many studies have provide us with conflicting data and treatment of a PDA has not resulted in a decreased rate of these morbidities. The study is group related because a patent ductus arteriosus is a condition that specifically concerns newborn infants, especially preterms, without any known variability related to sex or ethnicity.

I. BACKGROUND

Controversy exists about the optimal management of a patent ductus arteriosus in preterm infants, especially in those born at a gestational age less than 28 weeks and/or a birth weight ≤ 1000 grams, due to a lack of evidence for or against different approaches (1-11).

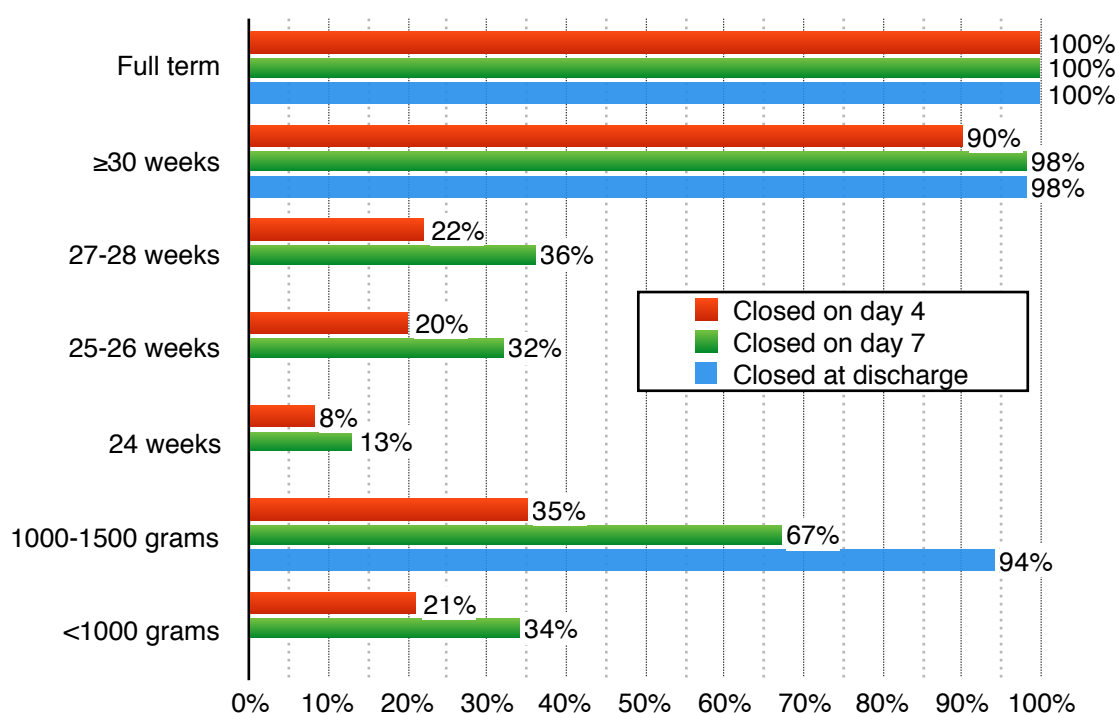
The reported incidence of a patent ductus arteriosus in preterm infants is between 30 and 60%, depending on the used definition, the timing of the diagnostics and studied population. The incidence of a PDA is lower after antenatal treatment with corticosteroids (12-14). Spontaneous closure of the ductus arteriosus can be delayed in case of intrauterine growth restriction (15-17), late onset septicemia (18), excessive fluid administration during the first days of life (19) and phototherapy (20, 21). Treatment with furosemide has been related to delayed ductal closure (22), although this association has not been found in other studies (23, 24). There is lack of consensus about the potential consequences of a PDA, the diagnostic criteria of a hemodynamically significant PDA (hsPDA) and the necessity of treatment of a hsPDA. This is expressed by the large variation in the management of a PDA between centers (25, 26). Large differences exist in the selection of patients that are treated, the timing of treatment, the modality of treatment, and the used drug dosage.

PDA is associated with major morbidities, such as pulmonary hemorrhage, intraventricular hemorrhage, necrotising enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity, and mortality and the aim of treatment of a PDA in preterm infants is to prevent morbidity and mortality on the short and long term. Great heterogeneity exists in the management of a PDA among neonatologists, where the reported percentage of treatment of preterm infants vary per site from 0% to 100% (7, 25).

Closure of the ductus arteriosus can be established by inhibition of the synthesis of prostaglandin with nonselective inhibitors of cyclooxygenase-1 and cyclooxygenase-2, such as indomethacin and ibuprofen, so-called COX-inhibitors (COXi).

In infants less than 28 weeks' gestation and/or with a birthweight ≤ 1000 grams the chance of spontaneous closure of the ductus arteriosus is about 30% (see Figure 1) and around 60% of these neonates will develop symptoms, such as hypotension, pulmonary edema, renal insufficiency or need for prolonged/increased respiratory support (7, 27, 28). After decades of clinical research the pivotal question still remains, are these symptoms causally related to the persistent patency of the ductus arteriosus or are these symptoms related to preterm birth, that by itself is associated with a higher incidence of a PDA? In other words, is the PDA the pathological causal factor of mortality and severe neonatal morbidity or should the PDA be considered as an epiphenomena, the so-called 'innocent bystander'?

Figure 1. Rates of spontaneous closure of the ductus arteriosus after birth in term and preterm infants (7).



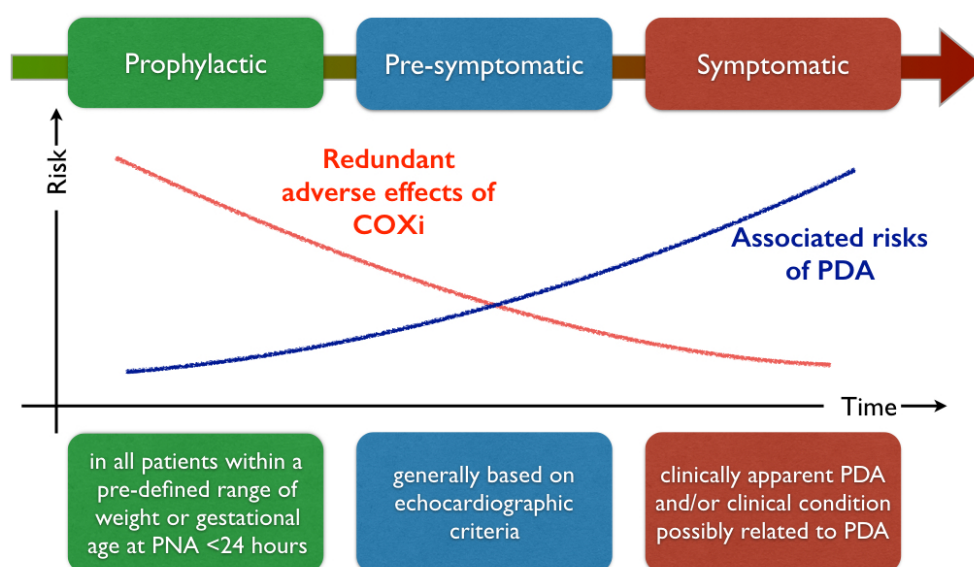
I.1. Management of a PDA in preterm infants

There are different approaches for preterm infants with a PDA, namely prophylactic, pre-symptomatic ('early'), symptomatic ('late') treatment and expectative management (8).

1. Prophylactic treatment implies the administration of COXi in all patients within a predefined range of weight or gestational age at a postnatal age less than 24 hours.
2. Pre-symptomatic ('early') treatment is based on risk stratification mainly with the use of echocardiographic markers of hsPDA, usually timed within the first 3-5 days of life.
3. Symptomatic ('late') treatment means that treatment is only started when there's a clinically apparent PDA and/or a clinical condition that might be related to a PDA.
4. Expectative ('conservative') management is characterized by 'watchful waiting' without the intention to actively close the ductus arteriosus.

As represented in Figure 2. the risk of redundant adverse events of COXi is decreasing as the postnatal age, at which COXi is started, increases, while vice versa the associated risks of a hsPDA increase.

Figure 2. Timing of treatment to actively close the patent ductus arteriosus



I.1.a. Prophylactic treatment

It has been shown that prophylactic administration of indomethacin reduces the incidence of symptomatic PDA, need for surgical ligation, and severe cerebral hemorrhage and it seems to reduce the risk of pulmonary hemorrhage (29, 30). However, no effect was found on mortality or neurodevelopmental outcome at the age of 18-36 months (31).

Prophylactic ibuprofen administration reduces the need for additional treatment, but no effect has been described on the incidence of (severe) intracranial hemorrhage or other relevant outcomes (32).

Prophylactic treatment is associated with the highest risk of redundant adverse effects of COXi, given the fact that in preterm infants a substantial portion of the patent ductus arteriosus would have closed without any specific intervention.

I.1.b. Pre-symptomatic or 'early' treatment

Large left-to-right shunting can already occur very early after birth. Clinical signs develop rather late with an average delay of 2 days (range 1-4 days) (33, 34). Echocardiography can be used in an effort to identify patients with an increased risk of PDA-related adverse outcomes (35). No beneficial effects on relevant neonatal morbidity were found in a systematic review of the administration of indomethacin for asymptomatic PDA in preterm infants (36).

I.1.c. Symptomatic or 'late' treatment

Another approach is to wait for a possible spontaneous closure of the ductus arteriosus. Treatment is only started when obvious clinical signs of a PDA have developed or a clinical condition that could possibly be

related to persistent ductal patency. The underlying pathophysiologic theory is that a PDA with significant left-to-right shunting results in pulmonary hyperperfusion and systemic hypoperfusion, respectively. The association of a PDA with an increased incidence of pulmonary hemorrhage, bronchopulmonary dysplasia and prolonged need of ventilatory support is ascribed to pulmonary hyperperfusion, whereas necrotising enterocolitis, renal failure, cerebral hemorrhage and periventricular leukomalacia are related to systemic hypoperfusion. It should be noted that these are associations and evidence of any causal relationship is lacking. As formulated by Evans 'Symptomatic treatment is the clinical approach that is most widely used but we do not have any evidence to support it' (8).

I.1.d. Expectative (conservative) management

Given the fact that in a substantial portion of preterm infants the ductus arteriosus will close spontaneously, in combination with lack of proven benefit of medical ductal closure from randomized controlled trials and systematic reviews (see § I.2.), an expectative approach to a PDA in preterm infants is gaining interest. Until now, no randomized controlled trial has been published that compares treatment of a PDA with cyclooxygenase inhibitors with an expectative approach, that is characterized by non-intervention in relation to the patent ductus arteriosus. Besides anecdotal data only 3 non-randomized cohort studies have been published (37-39). It concerns one prospective and two retrospective cohort studies in a relatively small study population. Vanhaesebrouck et al. published the results of a monocenter, prospective cohort study in which 30 preterm infants less than 30 weeks' gestation were included (37). All patients were mechanically ventilated and treated with surfactant for respiratory distress syndrome. A PDA was defined hemodynamically significant (hsPDA) when a transductal diameter >1.4 mm was found by echocardiography at a postnatal age of 48-72 hours. Ten out of thirty (33%) patients had a hsPDA, that was managed conservatively by fluid restriction (maximum of 130 mL/kg/day beyond the third day of life) and adjustment of the ventilatory settings (inspiratory time 0.35 seconds; increase PEEP to 4.5 cmH₂O). The ductus arteriosus was found to be closed in all these patients. Mortality rate and occurrence of major neonatal complications, such as necrotising enterocolitis, intraventricular hemorrhage (grade 3) and bronchopulmonary dysplasia, were not increased in comparison with data from the Vermont Oxford Network and the literature.

In an abstract by Sathiyamurthy et al. a monocenter, retrospective cohort study was described that included 270 ELBW infants (median GA 26 weeks; range 24-34 weeks) that were admitted within 72 hours after birth (38). In this center a PDA was only treated when a patient remained ventilator dependent. Only 16/270 (5.6%) of the preterms were treated with COXi (n=16) and/ or ligation (n=1). Following discharge 10/270 (3.7%) patients were treated medical or surgical. Relevant clinical outcomes were compared with the Vermont Oxford Network database, which revealed a significant reduction in PDA treatment (9.6% versus 52.3%; p=0.0001) and a significant reduction in bronchopulmonary dysplasia (28.9% versus 58.7%; p=0.0001). No statistically significant differences were observed in mortality, severe intraventricular hemorrhage and necrotising enterocolitis. However, there was a trend towards an increased incidence of necrotising enterocolitis.

Recently Rolland et al. published the results of monocenter, retrospective cohort study in which they evaluated the rate of spontaneous ductal closure in 103 preterm infants less than 28 weeks' gestation (39). The standard approach towards a PDA was conservative (no cyclooxygenase inhibitors; adjustment of ventilatory settings with low inspiratory time and high positive end-expiratory pressure; limited fluid intake of <140 mL/kg/day beyond the 3rd day of life). Twelve patients died within the first 3 days and were excluded from the analysis. In 59 of 91 (65%) infants, a spontaneous closure of the ductus arteriosus was observed. They report the following clinical outcomes: mortality (17%), bronchopulmonary dysplasia (35%), death or bronchopulmonary dysplasia (52%), necrotising enterocolitis (3%) and intraventricular hemorrhage > grade 3 (21%). Comparison of these outcomes with the Vermont Oxford Network data learns that the reported percentages of mortality, BPD and IVH in this study are higher (51). However, statistical significance could not be calculated from the available data.

In conclusion, convincing evidence about the safety of this approach is still not available. However, many centers have adopted this 'watchful waiting' approach without any report of increased mortality or relevant neonatal morbidity.

I.2. Randomized controlled trials regarding PDA management

We searched all randomized controlled trials evaluating PDA treatment in the US National Library of Medicine (Medline), Cochrane Library, EMBASE and ClinicalTrials.gov, using the Mesh terms: 'infant, newborn' AND 'ductus arteriosus, patent', that was combined with 'indomethacin' OR 'ibuprofen' OR cyclooxygenase inhibitors' OR 'paracetamol'. This search revealed a total of 787 hits. After screening 32 papers could be included in a systematic review (31, 40-70). Data on the outcome parameters were extracted independently by two reviewers and entered into Review Manager software for meta-analysis

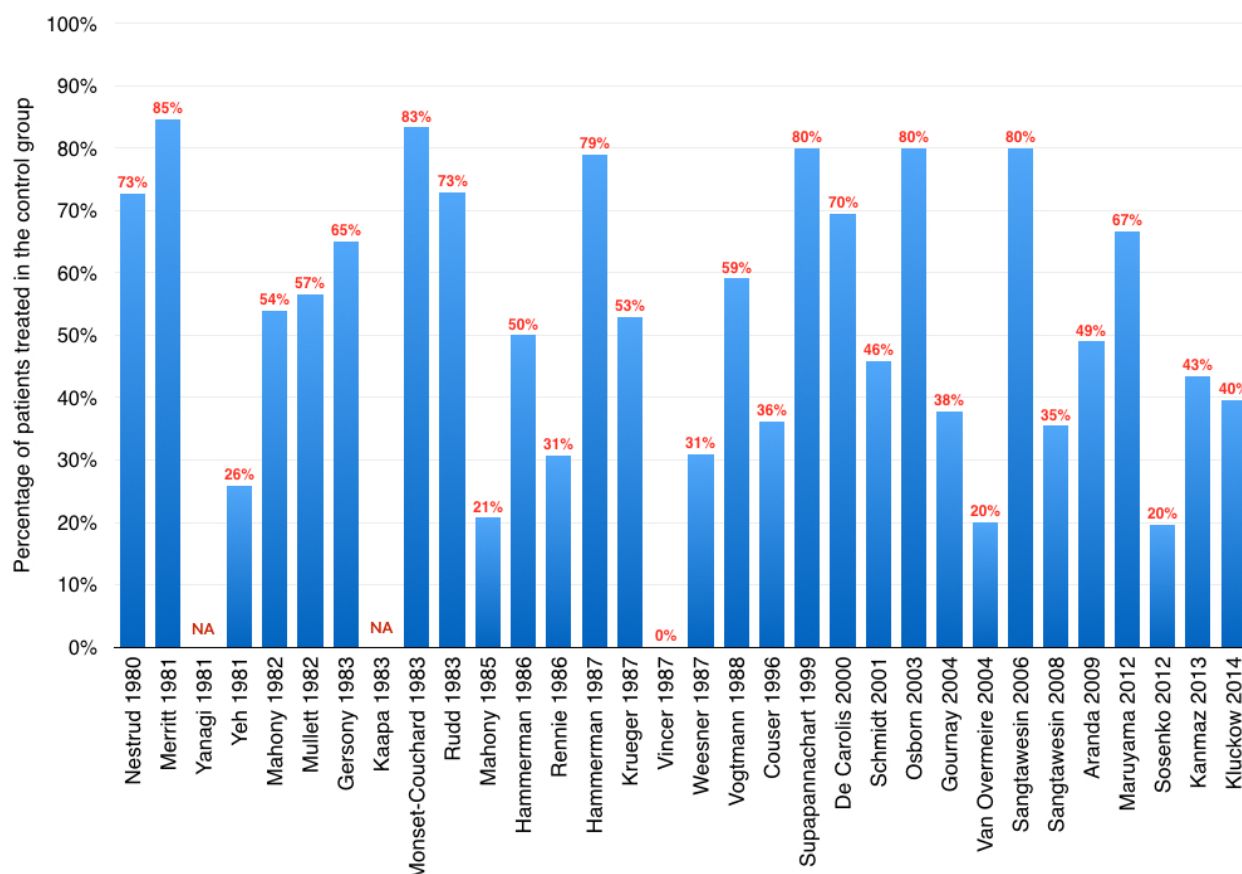
(Revman version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). All categorical outcomes are expressed as risk ratio with 95% confidence intervals. Meta-analysis of the 32 included studies showed that cyclooxygenase inhibitors are effective in ductal closure on the short term, since the risk ratio for failure of ductal closure is 0.44 (95%CI 0.38-0.50) in comparison with placebo. However, this ductal closure was found not to be associated with a reduction in mortality and major clinical outcomes: bronchopulmonary dysplasia, necrotising enterocolitis, intraventricular hemorrhage, and death or bronchopulmonary dysplasia (see Table 1).

Table 1. Meta-analysis 32 RCT's cyclooxygenase inhibition versus placebo in preterms with PDA

Outcome	Studies	Participants	Risk Ratio	95% CI
Mortality	31	3534	0.98	0.84 - 1.13
Bronchopulmonary dysplasia	23	3531	1.07	0.98 - 1.16
Oxygen need at PNA 28 days	16	1395	1.07	0.94 - 1.22
Oxygen need at PMA 36 weeks	8	2136	1.06	0.95 - 1.20
Necrotising enterocolitis	23	3285	1.05	0.83 - 1.32
Death or BPD (PMA 36 weeks)	7	2096	1.05	0.97 - 1.14
IVH	20	3150	0.98	0.88 - 1.10
Failure of ductal closure	23	1619	0.44	0.38 - 0.50

However, the conclusion that treatment of a PDA does to result in a significant reduction in mortality or (severe) neonatal morbidity is not entirely valid, since in 31 of the 32 studies a substantial portion of patients (20-85%) in the control group was actually treated with COXi and/or surgical ligation (see Figure 3).

Figure 3. Percentage of patients in the control group that actually are treated for a PDA



Instead of concluding that treatment of a PDA fails to reduce morbidity and or major morbidity, it can only be inferred from these randomized-controlled trials that there is no significant difference in early versus 'later' treatment, given the high crossover rate in the control groups in the above mentioned randomized controlled trials.

To our knowledge no randomized controlled trial has been published that investigates whether it is better to early treat a PDA in preterm infants or that a expectative approach is more appropriate.

Our **hypothesis** is that in preterms with a persistent ductus arteriosus an expectative management ("watchful waiting") is not inferior regarding the composite of mortality and/or NEC and/or BPD at a PMA of 36 weeks in comparison with an early treatment regime.

II. OBJECTIVE

To investigate whether in preterm infants, born at a GA less than 28 completed weeks, with a PDA (diameter >1.5 mm) an expectative management is not inferior to early treatment with regard to the composite of mortality and/or NEC (Bell stage $\geq$ IIa) and/or BPD at a PMA of 36 weeks.

III. STUDY DESIGN

The design is a multicenter, randomized, non-inferiority study conducted in neonatal intensive care units in the Netherlands and Belgium. The trial is anticipated to take 48 months.

IV. STUDY POPULATION

IV.1. Population

Preterm infants with a PDA, confirmed by echocardiography, admitted to a level III NICU. Outborn patients are also eligible.

IV.2. Inclusion criteria

- Gestational age < 28 completed weeks
- Postnatal age < 72 hours
- PDA diameter > 1.5 mm and ductal (predominantly) left-to-right shunt
- Signed informed consent obtained from parent(s) or representative(s)

IV.3. Exclusion Criteria

- Contraindication for administration of cyclooxygenase-inhibitors (COXi), such as:
 - active bleeding, especially intracranial or gastrointestinal hemorrhage
 - thrombocytopenia ($<50 \times 10^9/L$)
 - renal failure (raised creatinine ($>120 \mu\text{mol/l}$) or oliguria ($<0.5 \text{ mL/kg/h}$))
 - known or suspected necrotising enterocolitis
- Use of COXi prior to randomization
- Persistent pulmonary hypertension (ductal right-to-left shunt $\geq 33\%$ of cardiac cycle)
- Congenital heart defect, other than PDA and/or PFO
- Life-threatening congenital defects
- Chromosomal abnormalities and/or congenital anomalies associated with abnormal neurodevelopmental outcome

IV.4. Sample size calculation

The primary outcome parameter is the composite of mortality and/or NEC and/or BPD at a PMA of 36 weeks. Based on data from The Netherlands Perinatal Registry (PRN foundation; http://www.perinatereg.nl/home_english) the incidence of mortality, NEC and BPD is 20%, 10% and 15% respectively in preterm infants less than 28 weeks gestational age.

Non-inferiority is defined as a significant difference in the primary outcome parameter between the two arms of less than 10%. In other words, the 95%-confidence interval of the observed difference between an expectative approach and an early treatment should not exceed the non-inferiority margin of 10%. With an estimated a priori risk for the composite of mortality and/or NEC and/or BPD at 36 weeks of 35%, a type I error of 5%, a power of 80%, the sample size to exclude a non-inferiority margin of 10% for the difference in proportion of participants reaching the primary outcome parameter is 564 patients (282 per group). The normal distribution between the components of the primary outcome parameter, mortality, NEC and BPD, will be closely monitored by the Data Safety Monitoring Board, since a maximum difference in the primary outcome of 10% would obviously not be acceptable when it's for example solely based on a difference in mortality. This sample size was calculated using PASS 2008, version 08.0.8 NCSS (PASS 2008, NCSS, LLC. Kaysville, Utah, USA; www.ncss.com). Statistical significance is defined as a p-value <0.05 .

Based on retrospective data a total of 540 preterm with a gestational age less than 28 weeks will be born yearly, of which approximately 270 (52%) will have a PDA at a postnatal age of 24-72 hours. With an estimated inclusion rate of 66% the total number of included patients needed (564) will imply recruitment

during approximately 3.2 years in the Dutch centers (564/178) (see Figure 2). With the involvement of Belgian centers the total duration of recruitment will be shortened. With a conservative estimation of the contribution of each Belgian center comparable with the smallest Dutch centers (approximately 6.5% (see Figure 3) the recruitment time will be shortened from 3.2 years to approximately 2.5 years.

Figure 2. Estimated annual inclusions of patients

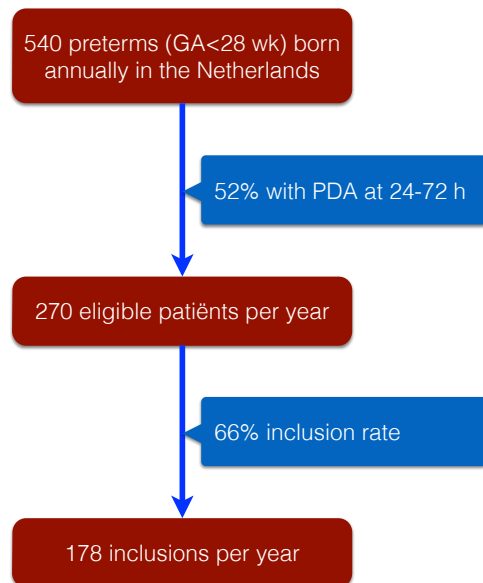
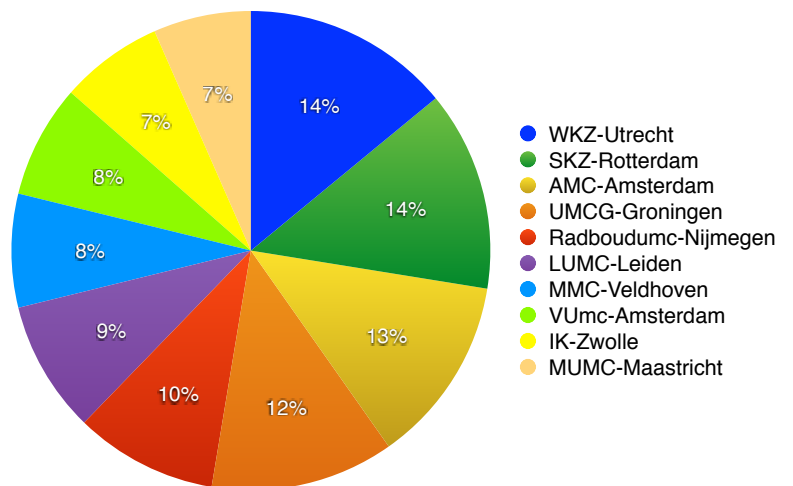


Figure 3. Contribution of each Dutch NICU in the total number of admissions annually

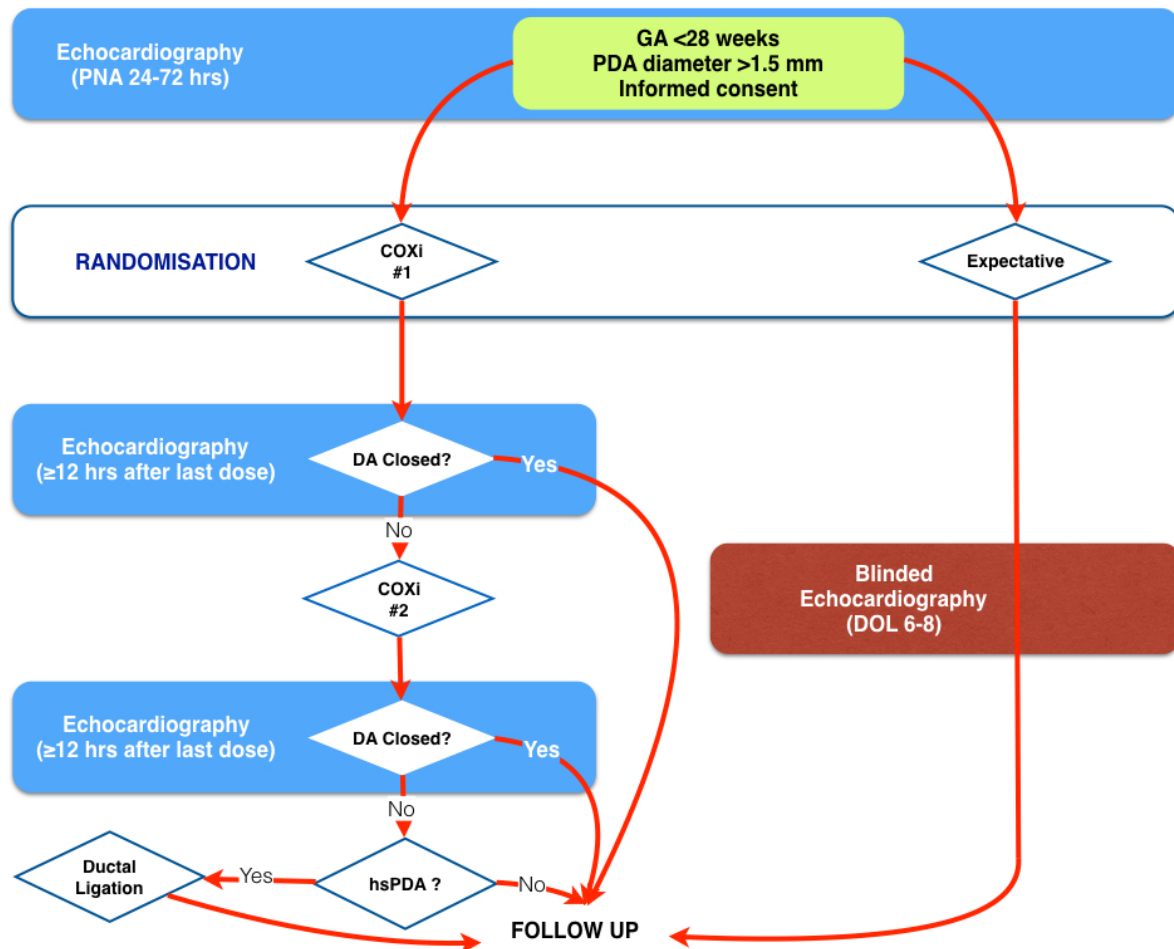


V. TREATMENT OF SUBJECTS

After obtainment of informed consent the first echocardiographic evaluation is performed at a postnatal age of 24-72 hours. In absence of exclusion criteria (see § IV.3.) patients will only be randomized when a PDA is present, the transductal diameter measures >1.5 mm and a blood flow pattern with a predominantly left-to-right shunt is observed. Randomization will assign the neonate to either the medical treatment (COXi) arm or the expectative PDA management arm.

It is essential that neonatal management is similar in both arms with the exception of the prescription of COX-inhibition and routine echocardiographic examination after a course of COXi in the medical treatment arm (see Figure 4).

FIGURE 4 - FLOW CHART STUDY PROCEDURES



V.1. Therapeutic details

V.1.a. Medical treatment arm

When the patient is allocated to the medical treatment arm COX-inhibition is prescribed and started as soon as possible.

We prefer to use Ibuprofen (IBU) for COX-inhibition in this study, since in comparison with indomethacin IBU seems to be as effective in ductal closure in preterm infants (71), reduces the risk of NEC and transient renal insufficiency (71), does not affect mesenteric blood flow (72-74), has less effect on renal perfusion (72-74), influences cerebral blood flow in a lesser extent (74-77), although IBU has not been shown to reduce the risk of ICH (30). Aside from the above mentioned reasons we are confronted with an actual lack of availability of indomethacin in most centers in the Netherlands and Belgium. However, Indomethacin (INDO) can be prescribed for medical ductal closure if this is preferred by a participating center.

The dosing schemes for IBU and INDO are according to the local guidelines.

For the first week of life the birth weight is used for calculation of the COX_i dosage. After a postnatal age of 7 days the actual weight is used for dose calculation, except when the actual weight is still less than the birthweight.

The treatment described above is considered standard of care in many NICU's worldwide. It should be noted that there is no modification of the commonly advised usage of IBU in this study. There are reports that suggest that an high dose of IBU might be more effective in ductal closure in preterm infants, especially in those less than 27 weeks' gestation (78-81). However, in a systematic review one refrained from recommendations regarding high dose IBU because of the limited number of patients enrolled in studies (71). The preferred route of administration of IBU is intravenously. However, this is at the disposal of the attending physician, since enteral administration appears at least as effective (71, 82-85).

Echocardiographic re-evaluation is performed at least 12 hours after the last (3rd) dose of the first COX_i course. If the ductus arteriosus is found to be closed, no further analysis or treatment is needed regarding the ductus arteriosus. A ductus arteriosus is considered to be closed when it can't be visualized using color Doppler imaging or when the transductal diameter measures less than 0.5 mm.

When the ductus arteriosus hasn't closed, a second course of COX-inhibition is started at least 24 hours after the third dose of the first course. COX_i dosages are similar to the first course.

Twelve to 24 hours after the last dose of the second course (6th gift) echocardiography is performed. If the ductus arteriosus is found to be closed, no further analysis or treatment is needed regarding the ductus arteriosus.

When the duct failed to close after two courses of COX_i (6 doses in total) and the PDA is judged to be still hemodynamically significant, ductal ligation can be considered, only when the so-called 'ligation criteria' are met (Table 2). This is based on the finding that standard ligation after failure of medical closure resulted in an increased incidence of BPD and neurodevelopmental impairment in comparison with delayed ligation in a selected population (86, 87).

Table 2 - Ligation criteria

I.	Exclusion of other causes of cardiovascular failure, such as sepsis, congenital heart defect et cetera
AND	
II.	Clinical findings of cardiovascular failure secondary to significant ductal left-to-right shunting <ul style="list-style-type: none">• Signs of systemic hypoperfusion<ul style="list-style-type: none">Refractory systemic hypotension and/orElevated serum lactate concentration (>2.5 mmol/L) and/or• Signs of pulmonary hyperperfusion<ul style="list-style-type: none">Prolonged ventilator dependency
AND	
III.	Echocardiographic findings of significant ductal left-to-right shunting <ul style="list-style-type: none">1. dPDA > 1.5 mm, and2. Unrestricted ductal left-to-right shunting ('pulsatile pattern'): end-diastolic flow velocity <50% of peak flow velocity, and/or3. End-diastolic flow velocity LPA > 0.3 m/s, and/or4. LA/Ao-ratio > 1.5
AND/OR	
1.	Severe left ventricular failure (mitral regurgitation), and/or
2.	Disturbed end-organ perfusion (retrograde diastolic blood flow in DAo)

V.1.b. Expectative PDA management arm

Patients randomized to the expectative management arm will not receive any COX_i and PDA management in this group can be characterized as "watchful waiting". This is not a unique approach, since a restrictive approach towards a PDA is increasingly used in many centers worldwide without the observation of an increased risk of neonatal mortality and morbidity, such as severe CLD, IVH, NEC and ROP (37, 38, 88).

It is essential that neonatal management is similar in both study arms with the exception of the prescription of COX_i and echocardiography at the end of the drug course in the medical treatment arm. It is of the upmost importance that NO extra interventions are to be undertaken with the intention to conservatively prevent or treat a (suspected) PDA in the expectative arm, such as fluid restriction and diuretics for that reason.

Moreover, it should be noted that there is insufficient evidence that fluid restriction and/or diuretics are of any benefit in patients with a (suspected) PDA (89, 90).

When during the first week the attending physician is of the opinion that the patient is in danger, when it's deprived from treatment with COXi, open label treatment can only be considered when the 'open label criteria' are met (see § V.1.c.).

V.1.c. Open label criteria for treatment with COXi in the expectative arm

It is essential in this study that patients, who are allocated to the expectative PDA management arm, are treated with the intention not to treat a patent ductus arteriosus and regard this condition as an 'innocent bystander'. Therefore, the use of COXi in the expectative PDA management arm is highly discouraged. Prescription of COXi in this expectative treatment arm can only be considered when the 'open label criteria' are met (Table 3).

Table 3 - Open label criteria

-
- | | |
|------|--|
| I. | Exclusion of other causes of cardiovascular failure, such as sepsis, congenital heart defect et cetera |
| AND | |
| II. | Clinical findings of cardiovascular failure secondary to significant ductal left-to-right shunting |
| | • Signs of systemic hypoperfusion |
| | Refractory systemic hypotension and/or |
| | Elevated serum lactate concentration (>2.5 mmol/L) |
| AND | |
| | • Signs of pulmonary hyperperfusion |
| | Prolonged ventilator dependency |
| AND | |
| III. | Echocardiographic findings of significant ductal left-to-right shunting |
| | 1. dPDA > 1.5 mm, and |
| | 2. Unrestricted ductal left-to-right shunting ('pulsatile pattern'): end-diastolic flow velocity <50% of peak flow velocity, and |
| | 3. End-diastolic flow velocity > 0.3 m/s, and |
| | 4. LA/Ao-ratio > 1.5 |
| AND | |
| | 1. Severe left ventricular failure (mitral regurgitation), and |
| | 2. Disturbed end-organ perfusion (retrograde diastolic blood flow in DAo) |
-

V.2. Use of co-intervention

All patients in this study will be treated according current (inter)national guidelines and local protocols regarding neonatal intensive care management.

Any use of COX-inhibitors in the expectative PDA management arm is discouraged, also for indications other than closure of the ductus arteriosus, if any.

Use of paracetamol has been associated with closure of a PDA in only a limited number of preterm infants (91-99). Moreover, the high dosage of 60 mg/kg/day of paracetamol that is used to close the ductus arteriosus is discouraged due concerns of safety and efficacy (100-102).

All prognostic relevant co-interventions and conditions will be monitored, as described in more detail in §VIII. 2.

VII. METHODS

VII.1. Study endpoints

VII.1.a. Main endpoint

The primary endpoint is the composite of:

- Mortality at a postmenstrual age of ≤ 36 completed weeks, and/or
- NEC (Bell stage $\geq$ IIa) at a postmenstrual age of ≤ 36 completed weeks, and/or
- BPD, defined as the need for supplemental oxygen at a postmenstrual age of 36 completed weeks

Necrotising enterocolitis is classified according the modified Bell staging criteria (see Table 4)(103).

Table 4 - Classification of necrotizing enterocolitis (modified Bell criteria)

Bell Stage	NEC classification	Signs
Ia	Suspected	Systemic: temperature instability, apnea, bradycardia, lethargy Abdominal: gastric retention, abdominal distension, emesis, heme-positive stool Radiographic: normal or intestinal dilation, mild ileus
Ib	Suspected	Systemic: same as stage Ia Abdominal: grossly bloody stool Radiographic: same as stage Ia
IIa	Definite, mildly ill	Systemic: same as stage I Abdominal: same as stage I, combined with absent bowel sound with or without abdominal tenderness Radiographic: intestinal dilation, ileus, pneumatosis intestinalis
IIb	Definite, moderately ill	Systemic: same as stage IIa, combined with mild metabolic acidosis and thrombocytopenia Abdominal: same as stage IIa, plus definite tenderness with or without abdominal cellulitis or right lower quadrant mass Radiographic: same as IIa, plus ascites
IIIa	Advanced, severely ill, intact bowel	Systemic: same as IIb, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular clotting, and neutropenia Abdominal: same as IIb, plus signs of peritonitis, marked tenderness and abdominal dissension Radiographic: same as IIa, plus ascites
IIIb	Advanced, severely ill, perforated bowel	Systemic: same as IIIa Abdominal: same as IIIa Radiographic: same as IIIa, plus pneumoperitoneum

Bronchopulmonary dysplasia is diagnosed following international standard criteria, including an oxygen reduction test according to Bancalari and Walsh (104, 105).

VII.1.b. Secondary endpoints

Secondary endpoints are short term sequela of cardiovascular failure, adverse effects during the stay in the hospital and long term neurodevelopmental consequences assessed at a corrected age of 2 years.

VII.1.b.1. Short term sequela of cardiovascular failure

- Hypotension (defined as MABP $<$ gestational age in completed weeks)
- Need for cardiovascular support (volume expansion, inotropes, vasopressors, corticosteroids et cetera)
- Pulmonary hemorrhage
- Total doses of COXi
- Adverse effects of COXi
- Need for surgical ligation of PDA

VII.1.b.2. Adverse effects during stay in hospital

- BPD at PNA of 28 days
- Mortality at PNA of 28 days and at hospital discharge
- Modes and duration of respiratory support and total days of oxygen supplementation
- Incidence of pulmonary air leakage (pneumothorax, pneumomediastinum, pulmonary interstitial emphysema)

- P/IVH, according the classification by Volpe (106)

Grade I	Germinal matrix hemorrhage with no or minimal intraventricular hemorrhage (<10% of ventricular area on parasagittal view)
Grade II	Intraventricular hemorrhage (10-50% of ventricular area on parasagittal view)
Grade III	Intraventricular hemorrhage (>50% of ventricular area on parasagittal view; usually distends lateral ventricle)
Separate notation	Periventricular echodensity (location and extent)

- PVE, according the classification by Hashimoto et al. (107)

Grade 0	No periventricular echogenicity
Grade I	PVE showing <u>less</u> echogenicity than that of the choroid plexuses (CPE)
Grade II	PVE showing <u>equal</u> echogenicity to that of the choroid plexuses (CPE)
Grade III	PVE showing <u>more</u> echogenicity than that of the choroid plexuses (CPE)
Cystic PVL (cPVL)	Periventricular cystic lesions (>3 mm) are observed

- NEC (Bell classification, see Table 4)
- Gastrointestinal bleeding
- Spontaneous intestinal perforation
- Time to full enteral feeding
- Sepsis (positive blood culture and antibiotics)
- ROP, according the international classification (108)
- Length of hospitalization

During the first 11 postnatal days there will be a daily recording in the eCRF of the following, first available parameters in the morning:

- Blood pressure (systolic, diastolic & mean blood pressure, in mmHg)
- Heart rate (in bpm)
- Urine output (in mL/kg/h in the last 8-12 hours)
- Actual weight (in grams)
- Total daily fluid intake (in mL/kg/24h)
- Total enteral intake (in mL/kg/24h)

VII.1.b.3. Long term health and neurodevelopmental outcome at 24 months

- Biometrics (weight, length and head circumference)
- Pediatric examination
- Neurologic examination, according Ariel Tison / Touwen / Hempel
- Cognitive assessment: BSID-III-NL
- Behavioral assessment: CBCL / TRF questionnaire
- Motor function: AIMS; Movement ABC 2-NL

All primary and secondary outcome parameters are evaluated as part of routine care in the Netherlands and Belgium.

VII.1.c. Health economic endpoints

VII.1.c.1. Cost Effectiveness Analysis (CEA)

General considerations - This study investigates the potential efficiency of expectative management of PDA in preterms with a PDA compared to usual care for preterms with a PDA. The usual care is heterogeneous. The cost-effectiveness analysis is performed from a societal perspective. The rationale behind hypothesizing that expectative management is the cost-effective alternative is that it saves on medical treatments and diagnostics at equal/non inferior effectiveness. The economic evaluation is based on the general principles of a cost-effectiveness analysis and is performed along-side the (randomized) clinical

study. Primary outcome measures for the economic evaluation, considering the 24 months follow-up period, are costs (direct and indirect), and composite survival and/or NEC and/or BPD. When the composite survival and/or NEC and/or BPD does not differ (as anticipated) between watchful waiting and usual care the cost-effectiveness decision rule will be cost minimization, else it will be cost associated with a gain or loss in survival and/or NEC and/or BPD. This efficiency outcome will be computed and uncertainty will be determined using the bootstrap method. If a difference between the two alternative treatments occurs a cost-effectiveness acceptability curve will be derived that is able to evaluate efficiency by using different thresholds (Willingness To Pay) for a combined survival effect. The impact of uncertainty surrounding deterministic parameters (for example prices) on the efficiency outcome will be explored using one-way sensitivity analyses on the range of extremes.

Cost analysis - The cost analysis exists of two main parts. First, on patient (preterm) level, volumes of care will be measured prospectively over the time path of the clinical study using the clinical research forms (CRF) and/or medical records and the inpatient treatment facility's administration system to collect information on for example: consultation pediatric cardiologist, echocardiography, chest X-ray, medication, intensive care transport, ductal ligation, etc. Where relevant, (missing) entries in the CRF will be verified by data from the medical records or the inpatient treatment facility's administration system. Second per arm full cost-prices will be determined using the Dutch guideline (109) or else real cost prices via activity based costing or center specific cost information. Productivity losses for parents will be estimated using a patient-based questionnaire (iPCQ) adapted to parents (110). The friction cost-method will be applied following the Dutch guidelines (109). The cost analysis will be performed using a mixed model approach with center as random coefficient and potential confounders (if any) as fixed.

Patient outcome analysis - Given the assumption of non inferiority a significant difference in effect is not anticipated. The effect analysis adheres to the design of the randomized controlled trial and equals the primary outcome measure of this study.

VII.1.c.2. Budget Impact Analysis (BIA)

General considerations - The aim of this BIA is to assess the financial consequences of implementing watchful waiting (and substituting for usual care) in the Dutch health care system in the short-to-medium term from the budget holders perspective (for example, Health Care/VWS, Third party payers) (111). The population concerned are preterms (< 28 weeks) with a PDA. Impact of the expectative management/watchful waiting on prevalence and incidence will be investigated/updated by use of epidemiological data in the Dutch context. Current data point to about 270 preterms with a PDA in the Netherlands every year.

Cost analysis - A global average cost estimate for watchful waiting is about €89.000 per patient (hospital/IC cost only). This figure multiplied by the yearly number of preterms with a PDA gives a global impression of the magnitude of the budget impact, i.e., €24.000.000. The usual care for preterms with a PDA is €24.800.000 which provides in a yearly budgetary saving of about €800.000 per year. Considering the BIA of the watchful waiting versus the current/usual care treatment mix we will take into account market dynamics such as estimates of uptake of watchful waiting and substitution rates. At least the 4 scenario's presented in "Toelichting kosteneffectiviteitsanalyse en budgetimpact" resp. current care, immediate 100% watchful waiting, gradual implementation watchful waiting and partial implementation watchful waiting will be considered.

The BIA base-case perspectives are resp. societal, health insurance/third party payer and health care (Budgetair Kader Zorg (BKZ)) will be taken into account. Several of these cost are collected in the CEA. Both annual resource use (in terms of volumes consumed) and cost (volumes multiplied by prices) will be presented. Prices are linked to perspectives: societal-CEA based prices, BKZ-average rates according to NZA, for health insurance perspective also NZA average rates and for for example a local health care provider perspective specific passenger rates (passanten tarieven).

The BIA will be assessed through (decision analytical) modeling and analyzed, if possible, in a probabilistic way (see for example Garattini et al., 2011) (112).

Deterministic uncertainty concerning BIA Input such as perspective, pricing parameters, time horizon, uptake, etc. will be dealt with by generating the budget impact as a series of scenario analyses covering a relevant range of costs.

VII.1.d. Other study parameters

The following clinical details will be documented using the standard medical records:

- Administration of antenatal steroids
- Maternal disease (pre-eclampsia)
- Maternal medication, especially COXi
- Mode of delivery
- Multiple birth
- Duration of rupture of membranes prior to birth
- Gestational age at birth
- Birth weight
- Apgar scores at 5 minutes
- Umbilical blood gas analysis
- Resuscitation after birth
- Surfactant administration
- Postnatal steroids

VII.2. Randomization, blinding and treatment allocation

After screening of eligible patients written informed consent must be obtained from parents or caregivers prior to randomization. The first echocardiographic evaluation must take place at a PNA between 24 and 72 hours. Inclusion of a patient should be performed before a PNA of 72 hours.

When the patient is randomized in the medical treatment arm, COXi must be administered preferably within 3 hours after the confirmation of a PDA with a ductal diameter > 1.5 mm.

The randomization is coordinated centrally and web-based. This trial will be protected from selection bias by using concealed, stratified and blocked randomization. Randomization will be per center and stratified according to gestational age stratum (Stratum A: <26 weeks; Stratum B: ≥26 weeks). The block size will vary in a range from 4 to 8.

The intention is to randomize multiple birth infants independently, unless it is the explicit demand of parents/ caretakers to treat the siblings identically in the same study arm.

Is is obviously not possible to perform a blinded study, since it is a difference in intention between the two patient groups, namely on one side the intention to medically treat and close a PDA with COXi and on the other hand the intention to accept a PDA as a non-pathological phenomenon and not specifically aiming at active closure of the ductus arteriosus.

Patient characteristics will be collected from all eligible infants that were not included in this study in order to assess any potential bias in the inclusion of patients.

VII.3. Study procedures

After obtainment of informed consent the first echocardiographic evaluation is performed at a postnatal age between 24 and 72 hours. When the transductal PDA measures more than 1.5 mm and a predominantly left-to-right shunt is observed, the patient will be randomized to either the medical treatment arm (COXi) or the expectative PDA management arm (see Figure 4).

Table 4 - Study procedures

Procedure	Screening & Trial Entry	Active closure arm		Expectative Management Arm	PNA 4 weeks	PMA 36 weeks	Discharge	Corrected Age 6 months	Corrected Age 12 months	Corrected Age 24 months
		COXi #1	COXi #2							
Assessment of eligibility	1									
Informed consent										
Echocardiography	2									
Randomization	2									
Prescription of COXi		3	5							
Follow-up echocardiography		4	6				1 1			
Blinded echocardiography				7						
iPCQ parents					8			8	8	8
Pulmonary assessment					9	1 0				
Assessment of long-term health and neurodevelopment										1 2

Notes

- Screening and assessment of eligibility as soon as possible after birth
- First echocardiogram and randomization at a postnatal age between 24 and 72 hours
- Prescription of cyclooxygenase-inhibitors (COXi) **only in patients randomized to the active closure arm!**
- Follow-up echocardiogram after first course of COXi: ductal closure?
- Prescription of second course of COXi, only when the first course failed to close the ductus arteriosus
- Follow-up echocardiogram after second course of COXi: ductal closure? In case of closure failure: see criteria for consideration of ductal ligation (Table 2).
- Blinded echocardiogram (if feasible!) to assess ductal patency only in patients randomized to the expectative treatment arm
- Patient-based questionnaire (iPCQ) adapted to parents at a postnatal age of 4 weeks and a corrected age of 6, 12 and 24 months
- Assessment of supplemental oxygen need at postnatal age of 28 days
- Classification of bronchopulmonary dysplasia (oxygen reduction test)
- When ductal closure has not been documented, ductal patency is echocardiographically examined before discharge in both the active closure arm and expectative management arm
- Assessment of long-term health and neurodevelopment
 - Biometrics (weight, length and head circumference)
 - Pediatric examination
 - Neurologic examination, according Ariel Tison / Touwen / Hempel
 - Cognitive assessment: BSID-III-NL
 - Behavioral assessment: CBCL / TRF questionnaire
 - Motor function: AIMS; Movement ABC 2-NL

VII.3.a. Echocardiography

VII.3.a.1. Initial echocardiogram

The use of warm sterile ultrasound gel is recommended for imaging to prevent heat loss and the total duration of the initial scan should not be longer than 30 minutes. Focus should be on the acquisition of all the necessary views and it is preferred to analyse the images and measure all data after completion of the exam. Gentle handling of the preterm during scanning has been shown not to disturb cardiorespiratory stability (113, 114).

Patency of the ductus arteriosus is determined and transductal diameter is measured as described by Kluckow and Evans (115). Direct ductal imaging is performed in the high left parasternal view with color Doppler mapping. The color gain should be set to obtain an optimal color flow image within the course of the ductus arteriosus and to eliminate any peripheral color interference. In the presence of a PDA the point of maximum constriction must be determined, which is the minimal diameter of the color jet within the course of the ductus. This diameter is measured end-systolic by a frame-to-frame analysis of the video. The mean of 3 consecutive measurements is used as the final transductal diameter. Using this technique resulted in a coefficient of variation of 12% (115).

The transductal shunt flow is determined by visualization of the ductus arteriosus in the high parasternal view with color Doppler. The scale is adjusted to avoid aliasing. With PW-Doppler the PDA flow wave is acquired and the transductal shunt flow is classified as: (predominantly) left-to-right, bidirectional, or (predominantly) right-to-left

In addition to assessment of patency and diameter of the ductus arteriosus and the transductal shunt direction the following parameters are preferably examined (optional):

- LA/Ao-ratio
- LVEDD/Ao-ratio
- Transductal blood flow velocity
- End-diastolic / Peak systolic ductal blood flow velocity ratio
- Mean and end-diastolic flow velocity of LPA
- Presence of reversed DAA blood flow (DAA regurgitant fraction)
- Presence and direction of interatrial shunt
- Rp/Rs index - ratio of the PI of LPA to the PI of DAA
- End-organ diastolic blood flow pattern in celiac trunk, superior mesenteric artery, renal artery, and pericallosal artery (antegrade/absent/retrograde)

Echocardiographic pictures and movies are stored and collected for blinded re-analysis.

VII.3.a.2. Follow up echocardiography

Follow up echocardiography is indicated in the treatment arm group in order to check whether the ductus arteriosus has closed after a completed first or second course of COXi.

VII.3.a.3. Blinded echocardiography

In order to be informed about the natural course of ductal closure in patients randomized to the expectative management group echocardiography is performed at the end of the first week of life (DOL 6-8). However, it is not allowed to share the results of this scanning with the clinical team that takes care of the patient. When this is not feasible, no echocardiography should be performed in order to prevent any influence on decision-making by the clinical team.

VII.3.a.4. Echocardiography before discharge

When ductal closure has not been documented before discharge, ductal patency is echocardiographically examined in both the active closure arm and expectative management arm.

VII.3.b. Patient-based questionnaire parents (iPCQ)

For the purpose of the cost effectiveness analysis the productivity losses for parents will be estimated using a patient-based questionnaire, that is adapted to parents. Parents are asked to fill in a specific questionnaire, i.e. the 'iMTA Productivity Costs Questionnaire' (iPCQ), at a postnatal age of 4 weeks and a corrected age of 6, 12 and 24 months, respectively (110). The questionnaire is given or sent to the parents by mail together with a post paid envelope or via electronic mail.

VII.3.c. Pulmonary assessment

Bronchopulmonary dysplasia is diagnosed following international standard criteria, including an oxygen reduction test according to Bancalari and Walsh (104, 105).

VII.3.d. Neonatal follow up program

All patients in this study will be included in the National Neonatal Follow Up Program and are therefore seen at a corrected age of 24 months. Their long-term health and neurodevelopment is assessed according the guideline and consists of:

- Pediatric (& neurologic) examination
- Cognitive assessment: BSID-III-NL
- Behavioral assessment: CBCL / TRF questionnaire
- Motor function: Movement ABC 2-NL

VII.4. Withdrawal of individual subjects

If they wish, parents or caregivers can leave the study at any time for any reason without any consequences. Patients in the expectative PDA management arm that fulfill the criteria for open label treatment with COXi and/or surgical ligation will remain in follow up and are therefore not withdrawn from the study. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

VII.5. Replacement of individual subjects after withdrawal

Only patients that are withdrawn from the study on request of parents or caregivers will be replaced. The total number of patients that can be replaced is limited to 25.

VII.6. Follow-up of subjects withdrawn from treatment

Infants, that are redrawn from the study, will be treated according the standard of care, including regular follow up after discharge, including assessment of neurodevelopmental outcome (see § VII.3.d.).

VII.7. Premature termination of the study

An independent Data Safety Monitoring Board (DSMB) will monitor the study on safety aspects and recommend termination of the study, if necessary (see § VIII.4).

VIII. SAFETY REPORTING

VIII.1. Section 10 WMO

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

VIII.2. AEs and SAEs

VIII.2.a. Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the interventions in this study. All adverse events observed spontaneously by the parents or caretakers or observed by the investigator or his staff will be recorded.

VIII.2.b. Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect (not applicable in this study);
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

All SAEs will be reported, as described in the next paragraph (§VIII.2.c), by the coordinating principle investigator to the Data Safety Monitoring Committee (DSMC) and through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, according the requirements of that METC.

VIII.2.c. Context-specific SAE reporting

This study population (critically ill preterm infants) has a high risk of serious complications (so-called "context-specific SAE's"), which are inherent to their vulnerable condition and unrelated to the intervention which is under evaluation in this trial.

These complications are included in the primary and secondary outcomes of this study and are recorded in the Case Report Form. This documentation will include the date of diagnosis, classification/gradation of the complication, type of action taken if appropriate (with some complications a wait and see approach is warranted). Since these complications are highly interrelated and of longitudinal character, it is impossible to indicate an exact date for the resolution or stabilization of each specific diagnosis. Therefore, we will use the date of discharge from the NICU for this purpose. As long as the child is admitted to the NICU, the complication will be classified as ongoing.

In light of the above, immediate and individual reporting of all these condition related complications will not enhance the safety of the study (116, 117). This is also in accordance with CCMO regulations: *'The research file may contain procedures in which is laid down that certain SAEs do not have to be directly reported, but may be listed in the periodic SAE line listings. This can be useful for certain types of studies'* (<http://www.ccmo.nl/en/saes-susars>).

The context-specific SAEs that will be identified, include the events listed under §VII.1.b of this protocol (secondary endpoints). An elective hospital admission will not be considered as a serious adverse event. It is the responsibility of the investigator in each participating center that every context-specific SAE is reported in the Case Report Form.

Once a year, an overview of the aforementioned complications for each treatment arm and ordered by organ system will be presented to the DSMB and METC by the coordinating investigator. This overview will consist of the following information: name of the complication, date of diagnosis, classification/gradation of the complication, type of action taken, date of discharge or ongoing.

VIII.3. Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated. According to the standard of care, all infants will participate in the usual NICU follow-up program. This program is targeted at evaluating and coordinating diagnostic procedures and treatment of all prematurity related problems, in close cooperation with regional and local pediatricians.

SAEs need to be reported till end of study, as defined in the protocol.

VIII.4. Data Safety Monitoring Board (DSMB)

An external Data Safety Monitoring Board will monitor safety outcomes and will provide the trial's Steering Committee with recommendations regarding continuing or stopping the trial (for all patients or subgroup of patients) when approximately 15%, 30, 50% and 75% of the anticipated outcome data are available. Data summaries for the DSMB will be prepared by a statistician who is not a member of the investigation team. The safety data will include, but not be restricted to, serious adverse events and the safety outcomes listed as secondary outcomes.

During the closed DSMB meetings, the data manager will be stand-by to reveal the allocation labels if the DSMB thinks this is necessary. The advice(s) of the DSMB will only be send to the sponsor of the study. If the DSMB recommends modification or cessation of the study protocol, this will be discussed with the Steering Committee, who will make a decision. Should the sponsor decide not fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

The DSMB will be composed of 3 individuals: a neonatologist with extensive knowledge about PDA, a statistician who has experience with clinical trials and a pediatric cardiologist with extensive knowledge about neonatal hemodynamics. The Steering Committee will propose a detailed mandate and review this with the DSMB. Identification and circulation of external evidence (e.g. from other trials or systematic reviews) is not the responsibility of the members of the DSMB. It is the responsibility of the coordinating principal investigator to provide any such information to the DSMB.

IX. STATISTICAL ANALYSIS

Treatment effects for the dichotomous clinical outcomes will be reported using risk ratio (RR) with 95% confidence intervals (CI). Normally distributed data will be presented as mean $\pm$ standard deviations, uneven distributed data as medians with interquartile ranges. Categorical data will be analyzed using the Chi-square for two- and multiway tables. Continuous data will be analyzed using the Student's t test. Statistical significance is set at $p < 0.05$. Both intention-to-treat and per-protocol analyses will be employed.

X. ETHICAL CONSIDERATIONS

X.1. Regulation statement

This study will be conducted according the principles of the Declaration of Helsinki (2013 version) and in accordance with the Medical Research Involving Human Subject Act (WMO).

X.2. Recruitment and consent

After admission of the newborn infant the parents will be informed about this study by the investigator, attending physician or research nurse. The *patient information letter* and *informed consent form* will be handed over. The parents/caregivers are given as much time as needed to consider their decision, although it will be explained that patients can only be included at a postnatal age between 24 and 72 hours. Whenever possible, we can inform the expectant mother and father already about the study during prenatal counseling.

X.3. Benefits and risks assessment, group relatedness

All patients in this study are treated according current (inter)national guidelines and local protocols regarding neonatal intensive care management. The administration of ibuprofen or Indomethacin does not pose an extra burden on the patient and is considered routine treatment in preterm infants with a PDA in a majority of neonatal intensive care centers. No extra investigations or interventions are needed in this study. Patients that aren't treated with COX_i are refrained from potential side effects of this drug. With the use of the 'NFU Hulplijn Risicoclassificatie' we classified the risk for the patients as negligible (118).

A restrictive approach towards a PDA is increasingly used in many centers worldwide without an concomitant increase in mortality or morbidity related to a PDA. No causal relationship has been proven between a (hemodynamically significant) PDA and the risk of conditions related to pulmonary hyperperfusion (f.e BPD and PH) and/or systemic hypoperfusion (f.e NEC, renal failure and PVL). Many studies have provide us with conflicting data and treatment of a PDA has not resulted in a decreased rate of these morbidities.

The study is group related because a patent ductus arteriosus is a condition that specifically concerns newborn infants, especially preterms, without any known variability related to sex or ethnicity.

X.4. Compensation for injury

The investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The sponsor has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

XI. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

XI.1. Handling and storage of data and documents

All data are handled confidentially and anonymously by the involved research group. Outcome data will be entered directly into eCRF's in a respecified database. It is possible to trace data to an individual subject with use of a subject identification code list. This code is not based on the patients name, initials and date of birth. All handling of data comply with the Dutch Personal Data Protection Act ('*Wet Bescherming Persoonsgegevens*' - WBP).

XI.2. Monitoring and Quality Assurance

The study will be monitored throughout its duration by means of personal visits to the Investigator's facilities and through other communications (e.g. telephone calls, web meetings, written correspondence). Monitoring visits will be scheduled at mutually agreeable times periodically throughout the study and at a frequency deemed appropriate.

At each site an 'initiation visit' will be organized during which all relevant documentation and training will be provided in order to participate safely and effectively in the trial.

Monitoring visits will be conducted to evaluate the progress of the study, ensure the right and wellbeing of the subjects are protected, check that the reported clinical study data are accurate, complete and verifiable from source documents, and that the conduct of the study is in compliance with the approved protocol and amendments, GCP and applicable national regulatory regulations. A monitoring visit consists a review of the essential clinical study documents (regulatory documents, CRFs, source documents, subject informed consent forms, et cetera). as well as discussion about the conduct of the study with the Investigator and staff. This will include 100% monitoring of patient informed consent forms and source verification on a proportion of CRFs (including 100% verification of the data collected from the first few patients recruited at each site). The Investigator and staff should be available during this visits to facilitate the review of the clinical study records and resolve/document any discrepancies detected during the visit.

The Sponsor's (or an authorized representative's) Quality Assurance department may conduct audits of all aspects of the clinical study either during or after the study has been completed. By participating in this trial the investigator agrees with this requirement.

The clinical study may also be subject to inspection by regulatory authorities, as well as the accredited Medical Ethical Committee/competent authority to ascertain that the study is being or has been conducted in accordance with protocol requirements, GCP guidelines, as well as the applicable regulatory requirements.

XI.3. Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

XI.4. Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

XI.5. End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination.

Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

XI.6. Public disclosure and publication policy

This study is registered with Netherlands Trial Register; identifier NTR5479 (www.trialregister.nl), which is equivalent to a ISRCTN number of the ISRCTN registry. at The study is also registered at ClinicalTrials.gov. (identifier NCT02884219).

The results of this study will be relevant for future patients, neonatologists and pediatricians both nationally and internationally. This study will provide valuable information on the treatment of a PDA in high risk preterm infants, which can be incorporated into national and international guidelines.

After completion of the study the results will be presented at scientific meetings and published in peer-reviewed open access medical journals.

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XI. APPENDICES

XI.1. Sites, local principal investigators and independent physicians

NICU Radboudumc Nijmegen (RUMC)	
Local PI:	Dr. W.P. de Boode, neonatologist, willem.deboode@radboudumc.nl
Independent physician:	Dr. M. Schreuder, pediatric nephrologist, michiel.schreuder@radboudumc.nl
Adress:	Geert Grooteplein-Zuid 10, 6525 GA Nijmegen, The Netherlands
NICU University Medical Center Groningen (UMCG)	
Local PI:	Mw. dr. E. Kooi, neonatologist, e.kooi@umcg.nl
Independent physician:	Dr. B.W.M. Willemse
Adress:	Hanzeplein 1, 9713 GZ Groningen, The Netherlands
NICU Academic Medical Center Amsterdam (AMC)	
Local PI:	Dr. W. Onland, neonatologist, w.onland@amc.nl
Independent physician:	Mw. dr. A.M. Bosch
Adress:	Meibergdreef 9, 1105 AZ Amsterdam-Zuidoost
NICU Maastricht University Medical Center (MUMC)	
Local PI:	Dr. T. Mulder, neonatologist, t.mulder@mumc.nl
Independent physician:	TBA
Adress:	P. Debyelaan 25, 6229 HX Maastricht, The Netherlands
NICU Erasmus Medical Center Rotterdam (EMCR)	
Local PI:	Dr. J. de Klerk, fellow neonatology, j.deklerk@erasmusmc.nl
Independent physician:	TBA
Adress:	s-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
NICU Vrije Universiteit Medical Center Amsterdam (VUMC)	
Local PI:	Prof.dr. H. Lafeber, neonatologist, HN.Lafeber@vumc.nl
Independent physician:	TBA
Adress:	De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands
NICU Leiden University Medical Center (LUMC)	
Local PI:	Dr. R. Visser, neonatologist, r.visser@lumc.nl
Independent physician:	TBA
Adress:	Albinusdreef 2, 2333 ZA Leiden, The Netherlands

NICU University Medical Center Utrecht, Wilhelmina Children's Hospital (UMCU)	
Local PI:	Dr. D. Vijlbrief, neonatologist, D.C.Vijlbrief@umcutrecht.nl
Independent physician:	Dr. M.P. Hennus, paediatric intensivist
Adress:	Lundlaan 6, 3584 EA Utrecht, The Netherlands
NICU Isala Kliniek Zwolle (IKZ)	
Local PI:	Dr. S. de Tollaer, neonatologist, s.m.mulder@isala.nl
Independent physician:	TBA
Adress:	Dokter van Heesweg 2, 8025 AB Zwolle, The Netherlands
NICU Maxima Medical Center Veldhoven (MMC)	
Local PI:	Dr. K. Dijkman, neonatologist, k.dijkman@mmc.nl
Independent physician:	TBA
Adress:	de Run 4600, Postbus 7777, 5500 MB Veldhoven, The Netherlands
Hôpital Erasme - Cliniques Universitaires de Bruxelles (HEB)	
Local PI:	Prof.dr. B. van Overmeire, neonatologist, bart.van.overmeire@erasme.ulb.ac.be
Independent physician:	TBA
Adress:	Route de Lennik 808, 1070 Brussels, Belgium
Universitair Ziekenhuis Brussel (UZB)	
Local PI:	Prof.dr. F. Cools, neonatologist, filip.Cools@uzbrussel.be
Independent physician:	TBA
Adress:	Laarbeeklaan 101, 1090 Brussels, Belgium
Universitair Ziekenhuis Antwerpen (UZA)	
Local PI:	Dr. D. van Laere, neonatologist, david.VanLaere@uza.be
Independent physician:	TBA
Adress:	Wilrijkstraat 10, 2650 Edegem, Belgium
Universitair Ziekenhuis Leuven (UZL)	
Local PI:	Prof.dr. G. Naulaers, neonatologist, gunnar.naulaers@uzleuven.be
Independent physician:	TBA
Adress:	Herenstraat 49, 3000 Leuven, Belgium



BeNeDuctus
Trial

Multi-center, randomized non-inferiority trial of early treatment versus expectative management of patent ductus arteriosus in preterm infants

Protocol Summary

(Principal Investigator: Willem P. de Boode, MD PhD)

Background

Much controversy exists about the optimal management of a patent ductus arteriosus (PDA) in preterm infants, especially in those born at a gestational age <28 weeks and/or a birth weight ≤ 1000 grams due to a lack of evidence for or against different approaches. A PDA has been associated with serious complications. However, a common finding is that medical and/or surgical treatment of a PDA seems not to reduce the risk of mortality or major morbidity. This might be related to the fact that a substantial portion of preterm infants are treated unnecessarily, because the ductus arteriosus (DA) might have closed spontaneously without any specific intervention. An expectative approach is gaining interest, although convincing evidence is still missing.

Objective

To investigate whether in preterm infants <28 weeks' gestation with a PDA an expectative management is not inferior to early treatment with regard to the composite of mortality and/or necrotizing enterocolitis (NEC) and/or bronchopulmonary dysplasia (BPD) at a postmenstrual age of 36 weeks.

Design

Multicenter, randomized, non-inferiority study conducted in neonatal intensive care units.

Eligibility

Preterm infants with a PDA, confirmed by echocardiography, admitted to a level III NICU.

Inclusion criteria

- Gestational age < 28 completed weeks; postnatal age 24-72 hours
- PDA diameter >1.5 mm and ductal left-to-right shunt
- Signed informed consent obtained from parents or representatives

Exclusion criteria

- Contraindication for administration of cyclooxygenase-inhibitors (COXi)
- Persistent pulmonary hypertension (ductal right-to-left shunt $\geq 33\%$ of cardiac cycle)
- Congenital heart defect, other than PDA and/or PFO
- Life-threatening congenital defects
- Chromosomal abnormalities and/or congenital anomalies associated with abnormal neurodevelopmental outcome
- Use of COXi prior to randomization

Intervention

Randomization will assign the neonate to either the medical treatment (COXi) arm, in which the intention is to close the DA, or the expectative PDA management arm, in which the DA is considered to be an 'innocent bystander'.

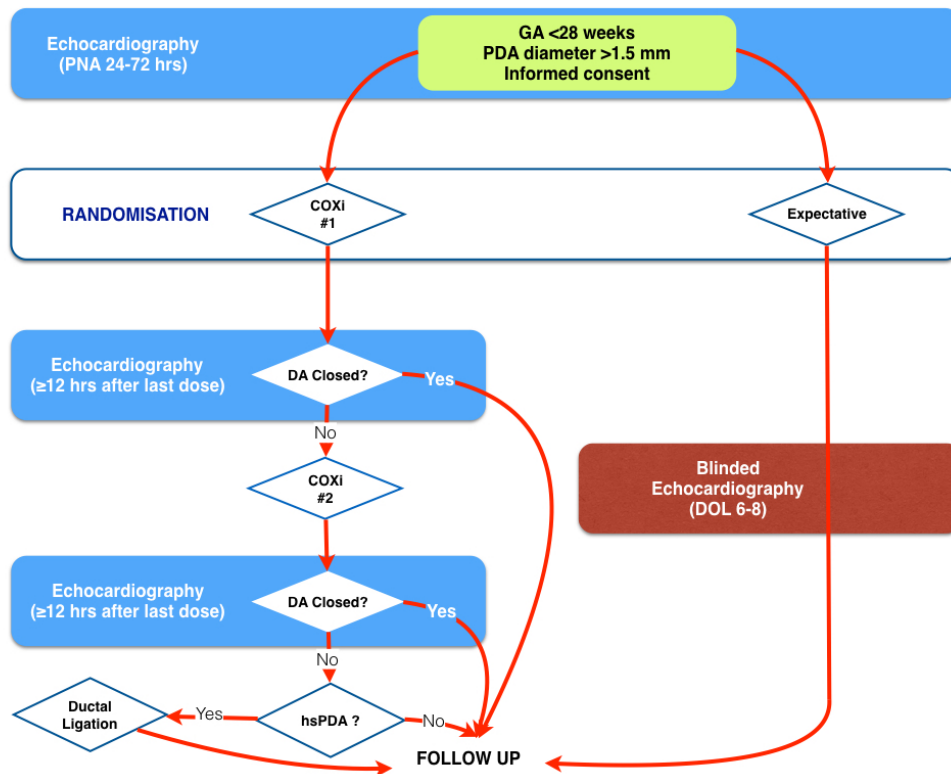
Primary outcome

The incidence of the composite of mortality, and/or NEC ($\geq$ IIa), and/or BPD, defined as the need for supplemental oxygen, all at a postmenstrual age of 36 completed weeks.

Secondary outcomes

- Short term sequelae of cardiovascular failure
- Adverse effects during the stay in the hospital
- Neurodevelopmental outcome, assessed at the corrected age of 24 months
- Health economics: cost effectiveness analysis and budget impact analysis.

Overview Study Procedures



Sample size calculation

Non-inferiority is defined as a significant difference in the primary outcome $<10\%$. With an estimated a priori risk for the composite of mortality and/or NEC and/or BPD at PMA of 36 weeks of 35% (based on retrospective data), a type I error of 5% and a power of 80%, a sample size of 282 patients is needed in each study arm (total 564 patients).

The normal distribution between the components of the primary outcome will be closely monitored by the Data Safety Monitoring Board.

Contact details

Willem P. de Boode, MD PhD (Project Leader)
Radboudumc Amalia Children's Hospital
Department of Pediatrics, Division of Neonatology (804)
Geert Grooteplein Zuid 10, 6525 GA Nijmegen, The Netherlands

Amalia Children's Hospital
Radboudumc

Phone +31 24 3614430
Mobile +31 6 21198028
Fax +31 24 3616428
Email willem.deboode@radboudumc.nl
Info beneductus.kg@radboudumc.nl
Web <http://neonatologynetwork.eu/studies/beneductus>

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Trial Register

NTR5479 (www.trialregister.nl)