**™›XProjectvoorstelformulier SUMMA OP2 Versie 2019-2020**

**NB: LEES DE OP1, 2, 3 INLEVERINSTRUCTIES GOED DOOR**

---

**1. Algemene gegevens:**

**Naam student:** Sergei Chin On
**E-mail adres:** s.j.chinon@students.uu.nl
**Studentnummer:** 6717187
**Jaar - maand aanvang SUMMA:** september 2019

**Naam begeleider (Principal Investigator, gepromoveerd onderzoeker):** Joppe Nijman
**Titel/functie:** Dr. / Kinderarts-intensivist en Postdoc
**E-mail adres:** j.nijman@umcutrecht.nl
**Afdeling of Instituut:** Kinder Intensive Care UMC Utrecht
**Divisie:** Kinderen

**Naam dagelijks begeleider:** Rian Bosch
**Titel/functie:** MSc/Promovendus
**E-mail adres:** r.bosch-5@umcutrecht.nl
**Afdeling of Instituut:** Kinder Intensive Care UMC Utrecht
**Divisie:** Kinderen

**Naam 2e lezer OP3 verslag:**
**(bij een stage buiten het UMCU is dit de interne UMCU begeleider)**
**Titel /functie:**
**E-mail adres:**
**Afdeling of Instituut:**
**Divisie:**

---

**Periode OP2:** **Periode OP3:**

**Tech Track? Nee**

---

**Beoordeling:**

**Inzet van de student tijdens OP2:** **voldoende / onvoldoende**

**Kwaliteit van het ingediende projectvoorstel:** **voldoende / onvoldoend**

**Handtekeningen**

| **Student:** | **Stagebegeleider (PI):** | **Interne UMCU begeleider (bij een stage buiten het UMCU** |
|---|---|---|
| **Naam:** Sergei Chin On | **Naam:** Joppe Nijman | **Naam:** |
| **Datum:** | **Datum:** | **Datum:** |

---

2. **Title**: Risk factors and outcomes of NEC in preterm and/or low birth weight infants with a congenital heart disease

---

3. **Scientific Abstract** (Max 300 words)

**Objective**: To identify the risk factors and outcome of necrotizing enterocolitis (NEC) in preterm (<35 weeks of gestational age) and/or low birth weight (LBW) (<2500 grams) infants with congenital heart disease (CHD) admitted to the neonatal or pediatric intensive care unit (NICU and PICU respectively) at multiple centra in Europe.

**Background**: NEC is an incompletely understood disease because of its complex and multifactorial pathogenesis. It is associated with high morbidity and mortality and occurs predominately in preterm and LBW infants. This predominance is increased when burdened with a CHD. Insights to risk factors, prognosis and better treatment strategies in the group of preterm and/or LBW infants with a CHD are lacking, therefore more studies are needed to improve the knowledge of these insights. This will enable better identification of patients with high NEC risk, improve clinical decision making, clinical management and ultimately improve the prognosis of these infants. This study aims to determine which variables in preterm and/or LBW infants with a CHD are associated with NEC.

**Study design**: A retrospective cohort study of preterm and/or LBW infants with CHD admitted to the NICU or PICU of four European centra between January 2015 and January 2020.

**Methods**: Data will be retrieved retrospectively from electronic health records of four European university academic centers (the UMC Utrecht (NL), the academic hospitals of Zurich (CH), Munich (GE) and Giessen (GE)) between January 2015 and January 2020. The data consist of the main study parameters/end points (NEC), maternal characteristics, neonatal characteristics and operation characteristics. Patients will be classified into the three Bell's NEC stadia (I-III) and control groups. Using univariate and multivariate analysis the risk factors for NEC will be identified.

**4. Line of research** (Maximum 500 words + max 10 references)

Priority program: Child Health – head prof. dr. C.K. van der Ent
Research program: Congenital and Hereditary Disorders – head prof. dr. M.J.N.L. Benders
Research theme: Pediatric Cardiac Critical Care

This project is embedded within the multidisciplinary clinical research program of Congenital and Hereditary Disorders, and more specifically the 'Congenital Heart Disease Life Span Program'. This is a unique life cycle approach with an extensive research program fully integrated in clinical follow-up from as early of 20 weeks gestation up to the age of 40 weeks and onwards. The researchers from this program participating in current project are: prof. dr. M.J.N.L. Benders, dr. K.A. de Bijl-Marcus (Neonatology), dr. J. Nijman, drs. V. Slooff, drs. R. Bosch (Pediatric Intensive Care), dr. J.M.P.J. Breur, dr. T. Steenhuis (Pediatric Cardiology), dr. K. van Loon (Pediatric Cardiac Anesthesiology) and dr. A. van Wijk (Pediatric Cardiac Surgery). Recent publications include "Early motor outcomes in infants with critical congenital heart disease", "The association of perioperative neonatal brain injury with school-age neurodevelopment in critical congenital heart disease" and "The characteristics of cerebral sinovenous thrombosis in neonates undergoing cardiac surgery".[1–3]

Furthermore, this a European multicentre project in which four centres of the European ABC consortium (Acquired Brain injury in Congenital heart disease, ABC) will be participating: the PI of current project (dr. J. Nijman) is supervising the "preterms with CHD" study group of this consortium, together with dr. W. Knirsch, a pediatric cardiologist from the university hospital of Zurich. The consortium has been working on several topics related to the neurodevelopmental outcome of neonates with congenital heart disease: in the first manuscript, which is currently submitted, the risk factors of perioperative brain injury in critical congenital heart disease are described based on data from the five participating centres.

Recently, the NECTAR study (Necrotizing Enterocolitis in Congenital Heart Disease) was initiated at the PICU with a NUTRICIA grant. This study is supervised by dr. J. Nijman and performed by PhD student R. Bosch. In this study, it is aimed to prospectively evaluate novel perfusion monitoring modalities (e.g. sequential doppler measurements of the arteria mesenterica superior) with respect to the development of NEC in neonates with critical congenital heart disease.


1. Stegeman R, Sprong MCA, Breur JMPJ, et al. Early motor outcomes in infants with critical congenital heart disease are related to neonatal brain development and brain injury. *Developmental Medicine & Child Neurology*. Published online August 20, 2021. doi:10.1111/dmcn.15024
2. Claessens NHP, Algra SO, Ouwehand TL, et al. Perioperative neonatal brain injury is associated with worse school-age neurodevelopment in children with critical congenital heart disease. *Developmental Medicine & Child Neurology*. 2018;60(10). doi:10.1111/dmcn.13747
3. Claessens NHP, Algra SO, Jansen NJG, et al. Clinical and neuroimaging characteristics of cerebral sinovenous thrombosis in neonates undergoing cardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery*. 2018;155(3). doi:10.1016/j.jtcvs.2017.10.083

**5. Project description** (Maximum of 2 pages plus 1 page for references)

**Background and rationale**

NEC is a common gastrointestinal disorder in the neonatal period and is characterized by ischemic necrosis of the intestinal mucosa which may progress to sepsis and even death in severe cases. NEC affects preterm and low birth infants most commonly, it has a prevalence of about 5% in very preterm and very low birth weight infants and a prevalence of about 10% in extremely preterm and extremely low birth weight infants.[4]

In the past years clinical outcomes for infants with NEC have fortunately improved due to earlier recognition and more aggressive treatment but with mortality rates in these infants ranging from 15% to 30%, mortality remains high.[5,6] This because of challenges in the management most likely caused by the incompletely understood multifactorial pathogenesis of NEC.[4] Different features in demographics and presentation of NEC in term infants compared to preterm infants have caused researchers to suggest that NEC in these two populations are distinct diseases with distinct pathogenesis.[7] NEC in late preterm and term infants with normal birth weight (>2500g) is normally associated with predisposing or underlying conditions such as congenital heart disease, hypoxic encephalopathy, sepsis, hypotension and respiratory disease. Evidence suggests that NEC in the population of late preterm and term infants with normal birth weight is mostly a disease of ischemic or hypoxic origin.[8] Preterm infants and or infants with low birth weight on the other hand are more susceptible for NEC because of their inherent immaturity. Intestinal and immunological immaturity lead to more susceptibility for NEC.[9] This agrees with consistent reports that low gestational age and low birth weight are clear risk factors.[10] Many other risk factors for NEC have been identified in neonates, however experts disagree about the value and significance of the different factors. The only risk factors there was high agreement on were gestational age, birth weight and feeding (formula vs breast).[10,11] Studies have also found strong association between congenital heart disease (CHD) and NEC. CHD in term infants raises the risk for NEC by at least 10-fold and CHD in preterm/low birth infants raises the risk up to 100-fold compared to the general population of newborns .[12] In another study preterm infants with CHD and low birth weight had a 1.7 fold increase in risk for NEC compared to other patients admitted to a neonatal intensive care unit.[13] This increase is caused by mesenteric hypoperfusion seen in neonates with congenital heart diseases. Evidence suggest that these hemodynamic changes caused by CHD have an additive effect on the classic risk factors in preterm infants causing higher risk for NEC.[14] Preterm and/or LWB infants with CHD are therefore likely more vulnerable for NEC, this emphasizing the importance of prevention, treatment and management of this specific population. Unfortunately, published data concerning risk factors and outcomes of NEC in preterm and/or LBW infants with CHD are scarce. This study aims to identify risk factors and outcomes of preterm and/ or low birth weight infants with congenital heart disease who were admitted to the pediatric or neonatal intensive care unit of multiple European centers.

**Rationale:**

Many studies show that low birth weight and prematurity are consistent risk factors for NEC in the population of neonates without CHD. Other studies demonstrate that CHD is a main risk factor for NEC in the population of term neonates. Studies that investigate the risk factors of NEC in the population of preterm and/or low birth weight infants with CHD are lacking or show inconsistent results. Risk factors thus remain unclear this leads to uncertainty in determining patients at risk. This study aims to determine which clinical, laboratory and imaging parameters in preterm and/or low birth infants are associated with NEC in a multicenter population.

**Objective**

Primary objective

Which variables are risk factors for NEC in European preterm (<35 weeks gestational age (GA)) and/or low birth weight (LBW) (<2500 gram) infants with congenital heart disease (CHD)?

Secondary objectives

1. What is the prevalence of NEC in the European population of preterm and/or LBW infants with CHD?
2. What is the 1-year mortality rate for preterm and or LBW infants with NEC in this population?
    a. What is the 1-year mortality for preterm and/or LBW infants with NEC in this population that received surgical intervention?
    b. What is the 1-year mortality rate/overall survival of preterm and/or LBW in this population that did not receive surgical intervention for NEC?
3. What is the 1-year mortality and morbidity for preterm and or LBW in this population diagnosed with NEC stage I, II or III?

Study design: Retrospective cohort study

Study population: Preterm (<35 weeks of GA) and or LBW (<2500 gram) infants with CHD (excluding persistent ductus arteriosus) admitted to the neonatal or pediatric intensive care unit in Europe.

Study parameters/ endpoints: Necrotizing enterocolitis (bell's criteria I, II and III) and 1-year mortality

Nature and extent of the burden associated with participation, benefit, and group relatedness: none

**References:**


4. Patel BK, Shah JS. Necrotizing Enterocolitis in Very Low Birth Weight Infants: A Systemic Review. *ISRN Gastroenterology*. 2012;2012. doi:10.5402/2012/562594
5. Neu J, Walker WA. Necrotizing Enterocolitis. *New England Journal of Medicine*. 2011;364(3). doi:10.1056/NEJMra1005408
6. Samuels N, van de Graaf RA, de Jonge RCJ, Reiss IKM, Vermeulen MJ. Risk factors for necrotizing enterocolitis in neonates: a systematic review of prognostic studies. *BMC Pediatrics*. 2017;17(1). doi:10.1186/s12887-017-0847-3
7. Kinstlinger N, Fink A, Gordon S, et al. Is necrotizing enterocolitis the same disease in term and preterm infants? *Journal of Pediatric Surgery*. 2021;56(8). doi:10.1016/j.jpedsurg.2021.01.007
8. Bubberman JM, van Zoonen A, Bruggink JLM, et al. Necrotizing Enterocolitis Associated with Congenital Heart Disease: a Different Entity? *Journal of Pediatric Surgery*. 2019;54(9). doi:10.1016/j.jpedsurg.2018.11.012
9. Hunter CJ, Upperman JS, Ford HR, Camerini V. Understanding the Susceptibility of the Premature Infant to Necrotizing Enterocolitis (NEC). *Pediatric Research*. 2008;63(2). doi:10.1203/PDR.0b013e31815ed64c
10. Rose AT, Patel RM. A critical analysis of risk factors for necrotizing enterocolitis. *Seminars in Fetal and Neonatal Medicine*. 2018;23(6). doi:10.1016/j.siny.2018.07.005
11. al Tawil K, Sumaily H, Ahmed IA, et al. Risk factors, characteristics and outcomes of necrotizing enterocolitis in late preterm and term infants. *Journal of Neonatal-Perinatal Medicine*. 2013;6(2). doi:10.3233/NPM-1365912
12. McElhinney DB, Hedrick HL, Bush DM, et al. Necrotizing Enterocolitis in Neonates With Congenital Heart Disease: Risk Factors and Outcomes. *Pediatrics*. 2000;106(5). doi:10.1542/peds.106.5.1080
13. Motta C, Scott W, Mahony L, et al. The association of congenital heart disease with necrotizing enterocolitis in preterm infants: a birth cohort study. *Journal of Perinatology*. 2015;35(11). doi:10.1038/jp.2015.96
14. Partridge E, Rintoul N. Congenital heart disease (CHD) and necrotizing enterocolitis (NEC). *Progress in Pediatric Cardiology*. 2019;54. doi:10.1016/j.ppedcard.2019.101146
15. Dees E, Lin H, Cotton RB, Graham TP, Dodd DA. Outcome of preterm infants with congenital heart disease. *The Journal of Pediatrics*. 2000;137(5). doi:10.1067/mpd.2000.108568
16. Anderson JG, Rogers EE, Baer RJ, et al. Racial and Ethnic Disparities in Preterm Infant Mortality and Severe Morbidity: A Population-Based Study. *Neonatology*. 2018;113(1). doi:10.1159/000480536

## 6. Plan of Investigation (Maximum of 3 pages)

### 6.1 Study design:

Study design: Retrospective electronic health record review

Duration: Approximately 27 weeks

Setting: Patients admitted to the Neonatal or Pediatric Intensive care unit (NICU respectively PICU) of the UMC Utrecht (NL), the academic hospitals of Zurich (CH), Munich (GE) and Giessen (GE)

### 6.2 Study population:

**Population (base)**

All preterm and/or low birth weight infants (<35 weeks of GA and/or birthweight <2500 gram) with congenital heart disease (CHD) admitted in the NICU or PICU of four European centers (the UMC Utrecht (NL), the academic hospitals of Zurich (CH), Munich (GE) and Giessen (GE)) between January 2015 and January 2020

**Inclusion criteria**

- Admission in the NICU or PICU of one of the four centra between January 2015 and January 2020 [AND]
- Prematurity (<35 weeks GA) [AND/OR] low birth weight (2500 gram) [AND]
- Congenital heart disease (defined by the European Pediatric Cardiac Code list (IPCCC short list) by the AEPC).

**Exclusion criteria**

- CHD being (only) patent ductus arteriosus
- Incomplete electronic health record
- No parental approval for the use of subject data for scientific research
- No intention to treat approach within the first days of life due to CHD, pre – or dysmaturity or any other genetic/ extracardiac malformation

**Sample size calculation**

- All admitted infants will be evaluated.
- It is estimated that approximately 500 infants will be included. Using the 1:10 rule of thumb and the rough incidence of NEC (Bell's ≥2) in preterm infants with CHD of 9%, the measured the number of parameters that can be used in multivariable regression is 4.5 or 5 (rounded).
- The rough incidence of 9% was reported by Anderson et al. who studied preterm infants that were admitted in the NICU and Dees et al who studies the outcome of preterm infants with CHD.[15,16] These studies defined NEC as a Bell's criteria ≥2. In this study we plan to analyze at the classifications of NEC (Bell's 1-3), therefore the incidence of 9% used to make the estimation above is probably lower than the true incidence in our population.

### 6.3 Methods

**Study parameters/endpoints**

**Main study parameters (definitions)**

| | |
|---|---|
| Necrotizing enterocolitis | Yes/No<br>If yes: classification according to Bell's criteria<br>Bell's I: Suspected NEC<br>**Clinical signs:** abdominal distention, bloody stools, Emesis/Gastric residuals, apnea/lethargy<br>**Radiological signs**: Ileus/ dilation<br>Bell's II: Proven NEC<br>**Clinical signs:** As in stage I plus; Abdominal tenderness, absent bowel signs, metabolic acidosis, thrombocytopenia<br>**Radiological signs:** Pneumatosis intestinalis and/or portal venous gas<br>Bell's III: Advanced NEC<br>**Clinical signs:** As in stage II, plus hypotension, significant acidosis, thrombocytopenia/ disseminated intravascular coagulation, Neutropenia<br>**Radiological signs**: As in stage II, plus pneumoperitoneum |

**Study parameters/ characteristics**

Maternal characteristics:

| | |
|---|---|
| Age | In years |
| Ethnicity | |
| Multiparity | Yes/No/Unknown<br>If yes: Number of previous pregnancies |
| Maternal hypertension | Yes/No<br>If yes: in mmHg |
| Maternal infection | Yes/No |
| Antenatal steroids | Initial administration at least 48 hours before delivery: Yes/No/ Unknown |
| Cesarean section | Yes/No/Unknown |
| Indication Cesarean section | Fetal indication: Yes/No/Unknown<br>Maternal indication: Yes/No/Unknown |

Neonatal characteristics:

| | |
|---|---|
| Sex | Male/female |
| Gestational age | In weeks and days<br>&<br>Classification of prematurity<br>- Extremely premature: ≤28 weeks<br>- Very premature: ≤32 weeks<br>- Late premature: ≥34 and ≤35 weeks |
| Apgar score | 1 min score<br>5 min score<br>&<br>Apgar score <7 at 5 min: Yes/No |
| Arterial umbilical cord pH | In pH level<br>(Normal range from 7.18 – 7.38 pH) |
| Birth weight (grams) | Grams<br>Z-score<br>&<br>Classification of birth weight<br>- Low birth weight (LBW): <2500 grams<br>- Very low birth weight (VLBW): <1500 grams<br>- Extremely low birth weight (ELBW): <1000 grams |
| Growth | % birthweight increase:<br>- 1 month after birth<br>- 2 months after birth<br>- 3 months after birth |
| Head circumference | In centimeters<br>Z-score |
| Hemoglobin count | In mmol/L at:<br>- 0-1 months<br>- 1-2 months<br>- 2-3 months<br>- 3-6 months<br>- 6 months -1 year<br>- At time of NEC diagnosis<br>OR<br>Anemia (Hb <4.3 mmol/l) before NEC diagnosis |

| | |
|---|---|
| CHD prenatally diagnosed | Yes/No |
| Born in tertiary clinic | Yes/No |
| Associated noncardiac/genetic disorders | Anomalies without genetic abnormality: Yes/No/Unknown<br>Chromosomal abnormality: Yes/No/Unknown |
| Duct-dependent CHD | Yes/ No |
| Type of CHD (IPCCC hierarchical classification). Congenital anomaly of:<br>- Position or spatial relationship of thoraco-abdominal organs<br>- Atrioventricular or ventriculoarterial connection<br>- Mediastinal vein<br>- Atrium or atrial septum<br>- Atrioventricular valve or atrioventricular septum<br>- Ventricle or the ventricular septum<br>- Functionally univentricular heart<br>- Ventriculo-arterial valve or adjacent regions<br>- Great arteries including arterial duct<br>- Coronary arteries | Category and type of congenital heart disease written out |
| Risk classification CHD (Clancy score) | Class I: two-ventricle heart without arch obstruction<br>Class II: two-ventricle heart with arch obstruction<br>Class III: single ventricle heart without arch obstruction<br>Class IV: single ventricle heart with arch obstruction |
| 1-year mortality | Yes/No |
| Morbidity:<br>- Total hospitalization days (for sub analysis)<br>- Hospitalization days in NICU/PICU<br>- Neurodevelopment (Bayley scales)<br>- Weight and head circumference | Parameters evident after diagnosis of NEC. 1 year follow up |

**Circulation parameters**

| | |
|---|---|
| Heart rate<br>- Preintervention (last recording)<br>- During (lowest recording) | In beats per minute<br>OR<br>Classification: |

| | |
|---|---|
| - Post intervention (1 ,24 and 48 hours) | - Bradycardia: ≤100 beats per minute<br>- Normo-cardia: 100-190 beats per minute<br>- Tachycardia: ≥190 beats per minute |
| Blood pressure<br>- Preintervention (last recording)<br>- During (lowest recording)<br>- Postintervention (1, 24 and 48 hours) | In mmHg |
| Pulse oximetry<br>- Preintervention (last recording)<br>- During (lowest recording)<br>- Postintervention (1,24 and 48 hours) | Oxygen saturation in % |
| Transcutaneous or arterial blood gas $PO_2$ and $PCO_2$<br>- Lowest recording during intervention | In mmHg |
| Neonatal Echocardiography<br>- Before surgical correction<br>- After surgical correction | Ejection fraction in % |
| Lactate levels<br>- Preintervention<br>- Post intervention (1, 24 and 48 hours) | In mmol/l |
| Central-peripheral temperature difference (during intervention)<br>- Highest difference<br>- Lowest difference | In degrees Celsius |
| Urine output measurement<br>- Preintervention (last recording)<br>- Postintervention (between 24 and 48 hours) | In ml/kg/hour |

**Feeding:**

| | |
|---|---|
| Type of feeding: | Breast milk<br>Donor breast milk<br>Preterm formula<br>Combination of the above |
| Timing of initial feeding | In days after birth |

| | |
|---|---|
| Feeding advancement | Slow rate: 5 ml/kg/day<br>High rate: 10-20 ml/kg/day |
| Colostrum feeding | Yes/No |
| Feeding continuity | - Continuous feeding<br>- Intermittent bolus feeding<br>- Combination of continuous and intermittent feeding |
| Use of fortifiers in feeding | Yes/No<br>If yes:<br>- Human milk based or<br>- Bovine milk based |
| Probiotics | Yes/No |
| Acid suppression | Yes (defined as (es)omeprazole)/No |

**Surgical parameters:**

| | |
|---|---|
| Weight at surgery | Grams |
| Head circumference at intervention | Centimeters<br>Z-score |
| Age at intervention | Post menstrual age and chronological age in days |
| Type of intervention | According to local coding system (AEPC code) |
| Total time of cardiopulmonary bypass | Time in minutes |
| Total time of circulatory arrest | Time in minutes |

**Pre-operative parameters (operation for CHD)**

| | |
|---|---|
| Ventilation | - Duration of invasive ventilation in days<br>- Reason for intubation: Respiratory, Circulatory, Other<br>- If other reason; written out |
| Cardiopulmonary resuscitation (CPR) | - Need for chest compressions: Yes/No<br>- Need for adrenalin/cardioversion according to CPR protocol: Yes/No<br>- PMA and chronological age at first CPR |

| | |
|---|---|
| | - Duration of CPR in minutes<br>- Number of CPR's |
| Preoperative therapeutic cardiac catheterization | Yes/No<br>If yes: type of catheterization (diagnostic/therapeutic): written out.<br>Amount |
| Arrhythmias | Yes/No (If intervention took place)<br>If yes: type of arrythmia (written out) |
| Heart failure | Intubation due to circulatory insufficiency: Yes/No<br>Inotropics including Milrinon: Yes/No |
| Pulmonary hypertension | Echocardiographic signs: Yes/No<br>Inhaled nitric oxide (iNO) treatment: Yes/No |
| Other medication | - Diuretics: Yes/No<br>- Dialysis: Yes/No<br>- Prostaglandin: Yes/No (+ duration)<br>- Empiric antibiotics: Yes/No |
| Sepsis | Yes/No<br>If yes defined as C-reactive protein (CRP) >20 + positive blood culture OR ≥5 days of antibiotics |
| Seizures | Yes/No<br>If yes:<br>- Confirmed by (automated) electroencephalography: Yes/No<br>- Clinical manifestations: Yes/No<br>- Treatment: Yes/No |
| Cerebral ultrasound | - Intraventricular hemorrhage: Yes/No (grade if yes)<br>- Post-hemorrhagic ventricular dilatation: Yes/No<br>- Cystic periventricular leukomalacia: Yes/No<br>- Cerebellar injury: Yes/No |

**Post-operative parameters (operation for CHD)**

| | |
|---|---|
| Prolonged mechanical ventilation | - Duration of invasive mechanical ventilation in days<br>- Duration of non-invasive ventilation in days<br>- Total duration of ventilation in days |

| | |
|---|---|
| Bronchopulmonary dysplasia | Yes (Oxygen Treatment > 21% for at least 28 days) / No<br>If Yes: Grade (mild / moderate / severe) |
| Cardiopulmonary resuscitation (CPR) | - Need for chest compressions: Yes/No<br>- Need for adrenalin/cardioversion according to CPR protocol: Yes/No<br>- PMA and chronological age at first CPR<br>- Duration of CPR in minutes<br>- Number of CPR's |
| Extra Corporeal life support (ECMO) | Yes/No, If yes:<br>- Duration in hours<br>- Weaning from ECMO: successful/ unsuccessful |
| Low Cardiac Output syndrome | Yes/No<br>Yes, when in first 48 hours postoperatively:<br>- Inotropic (including milrinone) AND<br>- At least 2 consecutive lactates > 3mmol/l AND<br>- Urine output < 1mlkg/hr during 6h |
| Postoperative cardiac catheterization | Yes/No, if yes: type of catheterization (diagnostic/therapeutic): written out |
| Arrythmias | Yes/No (If intervention took place)<br>If yes: type of arrythmia (written out) |
| Pulmonary hypertension | Echocardiographic signs: Yes/No<br>iNO treatment: Yes/No |
| Other medication? | Diuretics: Yes/No<br>Antibiotics: Yes/No |
| Sepsis | Yes/No<br>If yes: defined as C-reactive protein (CRP) >20 + positive blood culture OR ≥5 days of antibiotics |
| Seizures | Yes/No<br>If yes:<br>- Confirmed by (automated) electroencephalography: Yes/No<br>- Clinical manifestations: Yes/No<br>- Treatment: Yes/No |

| | |
|---|---|
| Near-infrared spectroscopy (NIRS) monitoring (brain) | Values in percentages |
| Cerebral ultrasound | - Intraventricular hemorrhage: Yes/No (grade if yes)<br>- Post-hemorrhagic ventricular dilatation: Yes/No<br>- Cystic periventricular leukomalacia: Yes/No<br>- Cerebellar injury: Yes/No |

## 6.4 Ethical considerations

### Regulation statement

The study will be conducted according to 'gedragscode gezondheidsonderzoek' and in accordance with EU GDPR (General Data protection Regulation).

### Recruitment and consent

Informed consent cannot be required due to the patient numbers and the retrospective nature of the study according to the first exception of the Code of conduct for Medical Research section 5. The conditions in this study to which the exception can be applied are:

- The investigation serves general (public health) interests. The investigation is part of a larger ongoing study carried out by an institution of scientific research (University Medical Center Utrecht). The aim of both this investigation and the larger study is a publication.
- The investigation cannot be caried out without the supply of data in this form.
- The subjects have not objected to the use of this data. At admission to the NICU and PICU, parents were informed that medical data of their infants may be used anonymously for scientific research. Objection to the use of this data for scientific research is possible at any time.
- Identification of the data is prevented, see following chapter.

## Administrative aspects and publication

### Handling and storage of data and documents

All data will be handled confidentially and in accordance with the EU GDPR. A data management plan is published online in DMPonline (https://dmponline.dcc.ac.uk/).
In summary, data collection from the patient management data systems will be performed by applicant, supervised by a doctor doctor (and member of the medical team) and entered anonymously in electronic data capture tool, Castor®. Other investigators will only have access to the anonymized dataset in Castor®.
For reviewing purposes, subject data will be coded in Castor® with a record number. A subject identification code list containing hospital ID's linked with these record numbers will be stored in a secured folder, according to local regulations and safeguarded by data management of the

Department.
The data and subject identification code list will be kept for 15 years.

**Amendments**
Any amendments that may cause the investigation to fall within the scope of the WMO is submitted to the ethical committee that gave the non-WMO advice. The amendments are any changes made to the research after an ethical committee gave a non-WMO advice.

## 6.5 Intended statistical analysis

The dichotomous secondary parameters will be presented quantitatively (in numbers and percentages). Continuous variables will also be presented quantitatively (using mean or median, if appropriate with standard deviation or interquartile range, respectively). Categorical data (i.e. descriptive primary and secondary parameters) will be presented qualitatively.
Missing data will be entered as such.
Initially, descriptive statistics will be applied to all study parameters. With respect to the main study parameters, both univariate (Chi-square, T-test or Mann-Whitney U, depending on type of parameter and normality) and multivariate analysis (multiple logistic regression) will be performed. In general, a p-value of <0,05 will be considere statistically significant.

## 6.6 Time planning

| Task | 2021 | | | | | | | | | | | | | | | | 2022 | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Month | | | | | | | | | | | | | | | | Month | | | | | | | | | | | | | |
| | Sep | | | | Oct | | | | Nov | | | | Dec | | | | Jan | | | | Feb | | | | Mar | | | | Apr | |
| | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 |
| Literature research | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Monitor literature | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Development of research tools | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Data collection | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Finalization of data collection and cleaning of data | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Data analysis | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Final report writing | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Submit final report | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

## 6.7 Scientific goals

Project goals by the first half of the project are:

- To be familiarized with and know the correct use of the medical data bases EPD Metavision and HIX (mainly the former)
- To be finished with the development of the research tools (such as Castor)
- To be finished or in the final stage of data collection

Personal learning objectives

- Work collaboratively with other researchers, using listening and communication skills
- Become familiar with the use of research tools such as Castor
- Become familiar and have knowledge of the most used statistical analysis techniques and know when these are implemented
- Learn the correct interpretation of results from statistical/data analysis
- Be able to explain the results of statistical/data analysis in a clear and uncomplicated manner
- Improve my analytical skills during the research project by analyzing raw data and transforming it into an academic paper
- Improve my writing skills during the research project thanks to practice and suggestions from supervising team

## 7 Research impact (1/2 page)

NEC remains to be a devastating and unpredictable disease with high morbidity and mortality affecting both premature born infants and term infants with critical CHD. Because of the fulminant nature of NEC, it is unlikely that new treatment will lead to major breakthroughs in decreasing its high morbidity and mortality. A preventive approach is more likely to yield better results. The results of this study will hopefully aid in the development of preventive strategies and therefore reduce the incidence of NEC in the future. Furthermore, the result of this study will clarify which risk factors are associated with NEC in preterm and/or low birth weight infants with a congenital heart disease. The findings could allow clinicians to intervene in the case of modifiable risk factors and could also aid in the improvement of clinical care. Lastly the inclusion of data from different European centers can enable the recognition of practice-differences, this can create the opportunity to improve the quality of care for patients in Europe.
In the future the results of this study can also aid in the development of a validated prediction model to asses certain patients at risk and quantify their risk profiles. As follow-up of this study further investigation can be done to precisely define the etiology of NEC in this patient group.