Morbidity and mortality after anaesthesia in early life: results of the European prospective multicentre observational study, neonate and children audit of anaesthesia practice in Europe (NECTARINE)

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Supplemental file for online

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Supplementary Material provides additional detailed information about demographics and ancillary results.

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Supplementary Table A.	Medical history and clinical status at time of inclusion.
Supplementary Table B.	Type of surgical and non-surgical procedures.
Supplementary Table C.	Intraoperative cardiac arrest cases.
Supplementary Table D.	Incidence and cause for morbidity at 30 days and mortality at 30 and 90 days.
Supplementary Table E.	Status at 30 and 90 days follow-up.
Supplementary Table E.	Morbidity and mortality in cardiac versus non-cardiac surgery, and cardiac versus non-cardiac non-surgical procedures.
Supplementary Figure 1.	Relationship between centre workload and outcomes.

Supplementary Table A. Medical history and clinical status at time of inclusion

		Frequency (*n*)	Percent
Procedures performed		6542	100
History of apnea/respiratory support	No	2526	61.4
	Yes	4015	38.6
Intra-ventricular hemorrhage	No	6078	92.9
	Yes	463	7.1
History of ECMO	No	6480	99.1
	Yes	62	0.9
History of patent ductus arteriosus	No	5322	81.4
	Yes	1219	18.6
History of previous surgery	No	4911	75.1
	Yes	1631	24.9
Admission of child at time of inclusion	Home/ward	4226	64.6
	ICU	1812	27.7
	Another hospital	504	7.7
Respiratory status at time of inclusion	Spontaneous	5608	77.5
	On oxygen	409	6.3
	Non-invasive ventilation	173	2.6
	Intubated & ventilated	873	13.4
	ECMO	19	0.3
Medication	No medication	3778	57.8
	Sedative	178	2.7

	Hemodynamic support	28	0.4
	Other	1566	23.9
Site of anesthesia management	Operating room	6279	96
	ICU	263	4
Patient assessment at time of anesthesia	Respiratory problems	1194	18.3
	Cardiovascular problems	1404	21.5
	Metabolic problems	666	10.2
	Neurological problems	813	12.4
	Renal problems	462	7.1
ASA score at time of inclusion			
	I	757	11.6
	II	3148	48.1
	III	1923	29.4
	IV	670	10.2
	V	38	0.6

ICU: intensive care unit; ECMO: extracorporeal membrane oxygenator

Supplementary Table B. ***Repartition of surgical and non-surgical procedures***

SURGICAL PROCEDURES n=5200 (79.5%)	**n**	**%**
Gastro-intestinal surgery	**3215**	**61.8%***
Anorectal malformations	163	5.1%
Biliary atresia: Kasai procedure	30	0.9%
Choledochal cyst excision	6	0.2%
Diaphragmatic hernia	97	3.0%
Fundoplication	18	0.6%
Gastrostomy tube	37	1.2%
Inguinal Hernia Repair (unilateral or bilateral)	1408	43.8%
Intestinal obstruction	300	9.3%
Liver biopsy	9	0.3%
Necrotising Enterocolitis	115	3.6%
Oesophageal atresia with/without tracheo-oesophageal fistula	145	4.5%
Omphalocele/gastroschisis	128	4.0%
Pyloric stenosis	312	9.7%
Ileostomy/Colostomy	133	4.1%
Other	303	9.4%
Cardiac Surgery	**439**	**8.4%***
Arterial switch operation	41	9.3%
Blalock shunt	16	3.6%
Closure of PDA	81	18.5%
Coarctation	59	13.4%
Aortic arch hypoplasia	10	2.3%
Norwood procedure	17	3.9%
Pulmonary artery banding	27	6.2%
Tetralogy of Fallot	22	5.0%
Total abnormal venous return	9	2.1%
VSD or ASD or AVC	60	13.7%
Other	100	22.8%
Thoracic Surgery	**58**	**1.1%***
Congenital lung lesions (Cystic adenomatous malformation)	27	46.6%
Mediastinal mass	4	6.9%
Lobectomy	13	22.4%
Diaphragmatic plication	2	3.4%
Other	12	20.7%
Genitourinary surgery	**350**	**6.7%***
Peritoneal dialysis catheter	11	3.1%
Correction of ureteropelvic junction	28	8.0%
Cystostomy and other surgery on bladder	36	10.3%
Nephrectomy	9	2.6%
Nephroureterectomy/Pyeloplasty	39	11.1%
Pyelostomy/nephrostomy	34	9.7%
Orchidopexy/Torsion of testis	46	13.1%
Ovarian cyst	26	7.4%
Circumcision for medical reason	26	7.4%
Ritual circumcision	17	4.9%

Urethral valves	47	13.4%
Neuroblastoma	5	1.4%
Bladder exstrophy	2	0.6%
Other	24	6.9%
Neurosurgery	**333**	**6.4%**
Closure of myelomeningocele	45	13.5%
Exploration and decompression spinal canal	5	1.5%
Craniosynostosis	41	12.3%
Ventricular shunt	159	47.7%
Ventriculostomy	53	15.9%
Craniotomy for hematoma removal	11	3.3%
Other	16	4.8%
Ophthalmic Surgery	**140**	**2.7%**
Laser destruction of chorioretinal lesion	45	32.1%
Phaco-fragmentation & aspiration of cataract	50	35.7%
Probing of nasolacrimal duct	7	5.0%
Glaucoma	8	5.7%
Vitrectomy	4	2.9%
Other	25	17.9%
Ear Nose Throat Surgery	**340**	**6.5%**
Choanal atresia	16	4.7%
Cleft lip	161	47.4%
Intervention on larynx (laser and other surgery)	33	9.7%
Lingual frenotomy	27	7.9%
Repair and plastic operations on trachea	29	8.5%
Tracheostomy	24	7.1%
Palate surgery	16	4.7%
Other	34	10.0%
Orthopedic surgery	**204**	**3.9%**
Arthrotomy	15	7.4%
Clubfoot repair	107	52.5%
Excision of soft tissue lesion	8	3.9%
Internal fixation of bone	5	2.5%
Supernumerary digit (polydactyly)	28	13.7%
Tenotomy	25	12.3%
Other	15	7.4%
Dermatology surgery	**154**	**3%**
Biopsy of skin and subcutaneous tissue	15	9.7%
Excision of skin and subcutaneous tissue	29	18.8%
Incision with drainage of skin and subcutaneous tissue	50	32.5%
Operation on skin and subcutaneous tissue	60	39.0%

Legend: In case of multiple interventions in one child, the most relevant procedure is presented. * representing the percentage calculated for the total number of procedures.

NON-SURGICAL PROCEDURES (n=1341, 20.5%)	**n**	**%**
Angiography/embolization	31	2.3%
Biopsy	47	3.5%
Bronchoscopy	153	11.4%
Burns dressing	3	0.2%
Cardiac lab (Percutaneous valvuloplasty, Raskind procedure)	102	7.6%
CT-Scan	40	3.0%
Cystoscopy/vaginoscopy	73	5.4%
Gastroenterology	98	7.3%
Infiltration	34	2.5%
MRI (Magnetic rad. Imaging)	340	25.4%
Ophthalmologic examination/Laser	40	3.0%
Pericardial or pleural drainage	14	1.0%
PICC line/Central venous/Broviac	251	18.7%
Cast	49	3.7%
Laryngoscopy/ENT endoscopy	27	2.0%
Arthrography	7	0.5%
Scintigraphy	16	1.2%
Examination under general anesthesia	16	1.2%
Evoked potential	7	0.5%
Peripheral intravenous line	5	0.4%
Miscellaneous	10	0.7%

Supplementary table C. Characteristics of children requiring intraoperative cardiopulmonary resuscitation for cardiac arrest.

Type of surgery	**n = 8**
Cardiac catheterization in children with CHD	4
Ophthalmologic surgery for congenital glaucoma	1
Gastro-intestinal surgery for intestinal obstruction	1
Gastro-intestinal surgery for gastroschisis	1
Gastro-intestinal surgery for necrotizing enterocolitis	1

Supplementary Table D. Incidence and cause for morbidity at 30 days and mortality at 30 and 90 days

	n (%)		Incidence 95% CI
Morbidity at 30 days	**850 (16.3)**		**0.17 (0.16, 0.181)**
Respiratory complications	**457 (53.6%)**		0.091 (0.084-0.1)
ECMO	14		
Failure of weaning with prolonged ventilatory support	229		
Need for re-intubation after being extubated	71		
Pleural effusion	46		
Pneumonia	44		
Pneumothorax	53		
Surgical Complications	**329** (38.7%)		0.066 (0.059-0.073)
Re-operation for unsuccessful or complicated first surgery	178		
Severe surgical site infection with new onset of antibiotics	98		
Prolonged parenteral nutrition due to surgical complication	43		
Cardio-vascular complications	**315** (37%)		0.063 (0.056- 0.07)
Arrhythmia	70		
Episode(s) of cardiac arrest	50		
Cardiac ischemia (elevated troponin)	5		
ECMO	17		
Arterial/venous embolism	9		
Inotropes-vasopressors needed	223		
Venous thrombosis on central venous line	22		
Neurological complications	**146 (17.2%)**		0.029 (0.025, 0.034)
New onset of Hypertonia	13		
New onset of Hypotonia	20		
Intracranial bleeding confirmed by imaging	46		
Intracranial ischemia confirmed by imaging	26		
Occurrence of seizures (clinically or EEG)	59		
Renal insufficiency	**98 (11.5%)**		0.02 (0.016, 0.024)
Continuous renal replacement therapy	24		
Increase creatinine levels with adaptation of doses	67		
Peritoneal dialysis	17		
Liver failure	**51 (6.0)**		0.01 (0.008, 0.013)
Coagulation disorders (increase INR > 2)	27		
Increase serum bilirubin (>300 micromol/L or 10 mg/dl)	32		
Mortality at 30 and 90 days	**105**	**31**	**0.032 (0.027, 0.037)**
Sepsis	30	8	
MOF	22	5	
Cardiac failure	19	9	
Brain damage	11	3	
Palliative care	8	1	
Respiratory failure	7	3	
Pulmonary hypertension	2	-	
Metabolic disease	2	-	
	2	1	
	2	1	
	-	1	

Liver failure Coagulopathy and haemorrhage Unknown			

ECMO: extracorporeal membrane oxygenator; EEG: electroencephalogram; MOF: multiple organ failure

Supplementary Table E. Status at 30 and 90 days follow-up

	n (%)
Status at 30 days*	
Discharged to home	4172 (79.9%)
Still in hospital	407 (7.8%)
Discharged to another hospital	257 (4.9%)
Still in ICU	279 (5.3%)
Death	105 (2.0%)
Status at 90 days**	
Alive - discharged home before day 30	3494 (83.5%)
Alive - discharged home between 30 and 90 days	439 (10.5%)
Alive - still in Hospital at 90 days	220 (5.3%)
Death - between 30 and 90 days	31 (0.7%)
Readmission to the Hospital until 90-day follow-up	749 (18%)

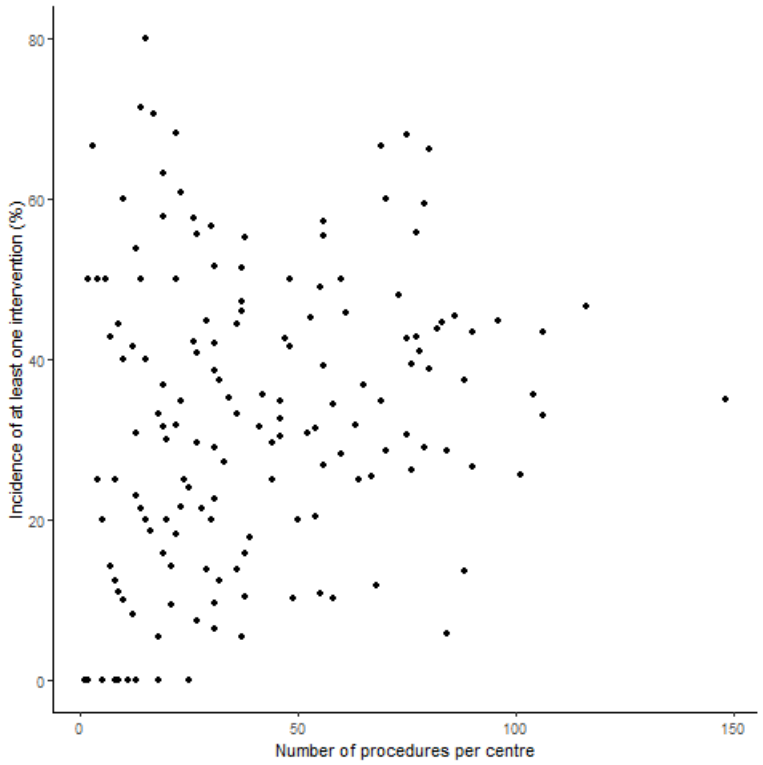
Legend: *Follow up data at 30 days was available for 93.3% of cases. **Follow-up data at 90 days was retrieved for 75% of the whole cohort. ICU: intensive care unit

Supplementary Table F. Morbidity and mortality in cardiac versus non-cardiac surgery, and cardiac versus non-cardiac non-surgical procedures.

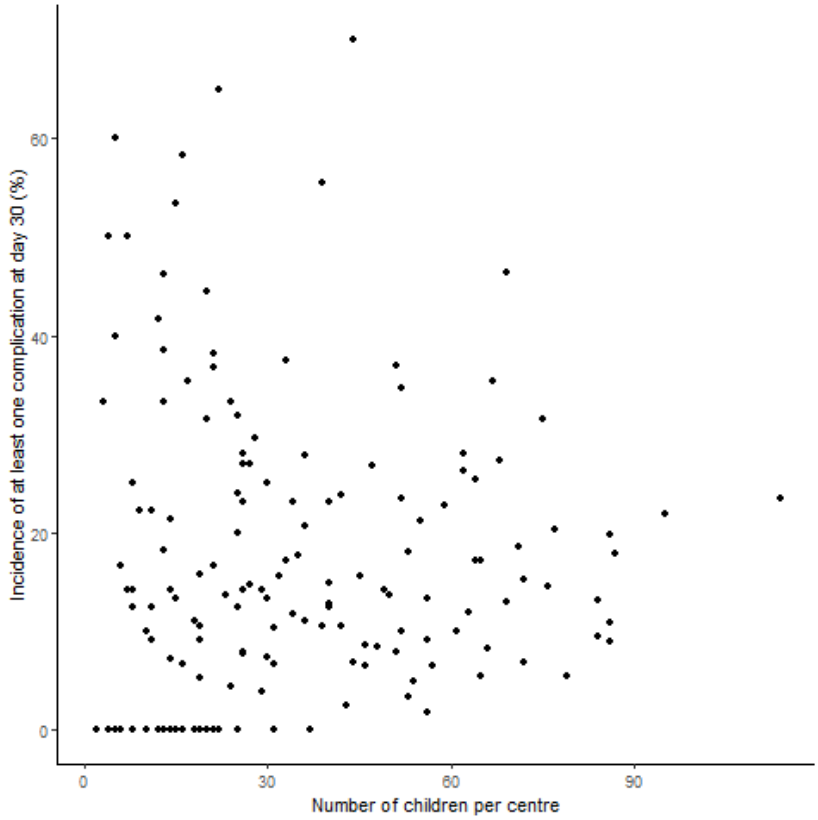
	30-Day Morbidity	30- & 90-day Mortality
Surgeries (non-cardiac)	0.139 (0.128, 0.151)	0.024 (0.019, 0.029)
Cardiac surgery	0.516 (0.459, 0.572)	0.095 (0.063, 0.135)
Non-surgical procedure (excluding cardiac catheterism)	0.176 (0.151, 0.204)	0.042 (0.029, 0.059)
Cardiac catheterism	0.15 (0.071, 0.266)	0.058 (0.012, 0.159)

Supplementary Figure 1. Relationship between centre workload and outcomes.

A: Incidence of at least one intervention and the number of procedures per centre.



B: Relationship between incidence of at least one complication at day 30 and number of children anesthetised in each centre



NECTARINE: NEonate – Children STudy of Anaesthesia pRactice IN Europe

Epidemiology of critical events, morbidity and mortality in neonatal anaesthesia:
A European prospective multicentre observational study

PROTOCOL ID: NECTARINE

Study protocol
Final 1.0

Dated 28 Aug 2015

ClinicalTrials.gov identifier # NCT02350348

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Sponsorship:

The NECTARINE study is entirely sponsored by a grant from the European Society of Anaesthesiology Clinical Trial Network (ESA CTN). The aim of the European Society of Anaesthesiology Clinical Trial Network is to provide an infrastructure for clinical research in the fields of Anaesthesia, Pain, Intensive Care and Emergency Medicine by transnational European collaborative studies.

No other institution or industrial company is or will be involved in financing, planning or conducting the study.

The Clinical Trial Network of the European Society of Anaesthesiology can be contacted via:

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Endorsement:

The NECTARINE study has been endorsed by the following societies/organisations:

- **ААУ-AAU:** Асоціація Анестезіологів України (Association of Anesthesiologists of Ukraine)
- **ADARPEF**: Association des Anesthésiste-Réanimateurs Pédiatriques d'expression française (Association of French speaking Paediatric Anaesthetists and Intensivists)
- **APAGBI**: Association of Paediatric Anaesthetists of Great Britain and Ireland
- **ČSARIM**: Česká společnost anesteziologie, resuscitace a intenzívní medicíny (Czech Society of Anaesthesiology and Intensive Care Medicine)
- **DGAI**: Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin (German Society for Anaesthesiology and Intensive Care Medicine)
- **EAS**: Eesti Anestesioloogide Selts (Estonian National Society of Anaesthesiology)
- **ESPA**: European Society for Paediatric Anaesthesia
- **HDAIL**: Hrvatsko društvo za anesteziologiju i intenzivno liječenje (Croatian Association of Anaesthesiology and Intensive Care Medicine)
- **HSA**: ΕΛΛΗΝΙΚΗ ΑΝΑΙΣΘΗΣΙΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ (Hellenic Sociey of Anaesthesiology)
- **LARD:** Lietuvos anesteziologu-reanimatologu draugijos (Lithuanian Society of Anaesthesiologists-Reanimatologists)
- **NAF:** Norsk Anestesiologisk Forening (The Norwegian Society of Anesthesiology)
- **NVA**: Nederlandse Vereniging voor Anesthesiologie (Netherlands Society of Anaesthesiologists)
- **NAF:** Norsk Anestesiologisk Forening (The Norwegian Society of Anesthesiology)
- **NVA-kids**: Sectie Kinderanesthesiologie (Society of Pediatric Anesthesia of the Netherlands)
- **ÖGARI**: Österreichische Gesellschaft für Anästhesiologie, Reanimation und Intensivmedizin (Austrian National Society of Anesthesia and Intensive Care Medicine)
- **PTAiIT**: Polskie Towarzystwo Anestezjologii i Intensywnej Terapii (Polish Society of Anaethesiology and Intensive Therapy)
- **S.A.R.N.eP.I.**: Società di Anestesia e Rianimazione Neonatale e Pediatrica Italiana (Italian Society for Paediatric and Neonatal Anaesthesia and Intensive Care)
- **SAY**: Suomen Anestesiologiyhdistys (Finnish Society of Anaesthesiologists)
- **SEDAR**: Sociedad Española de Anestesiología, Reanimación y Terapéutica del Dolor (Spanish Society of Anaesthesiology, Intensivists and Pain)
- **SFAI**: Svensk Förening för Anestesi och Intensivvård (Swedish Society of Anesthesia and Intensive Care Medicine)
- **SFAR**: Société Française d'Anesthésie et de Réanimation (French Society of Anaesthesiology and Intensive Care)
- **SGKA/SSAR**: Schweizerische Gesellschaft für Kinderanästhesie /Société Suisse d'Anesthésiologie et de Réanimation (Swiss Socity of Anaesthesiology and Intensive Care)
- **S.I.A.A.T.I.P.**: Societa' Italiana Di Anestesia, Analgesia e Terapia Intensiva Pediatrica, Italian Society of Anesthesia, Analgesia and Pediatric Intensive Care
- **SRATI**: Societatea Romana de Anestezie si Terapie Intensiva (Romanian Society of Anaesthesia and Intensive Care)
- **SPA:** Sociedade Portuguesa de Aanestesiologia (Portuguese Society of Anesthesiology)
- **UAIS - SAAI**: Udruženje anesteziologa i intezivista Srbike - Serbian Association of Anesthesiologists and Intensivists

1.2 Summary:

Despite recent advances, neonates remain at risk of life-threatening complications following general and regional anaesthesia, and there has been limited identification of clear predictive factors. Although several cohort studies report the incidence of perioperative anaesthetic complications, these are generally limited to reports from single centres. A prospective multicentre study "APRICOT" (Anaesthesia PRactice In Children: an Observational Trial (APRICOT)) was conducted in 2014 to establish the incidence of severe critical events in children requiring anaesthesia and to identify associated risk factors [ClinicalTrials.gov identifier # NCT01878760]. This ESA Clinical Trial Network project collected data from over 30,000 patients (aged from birth to 15 years of age) across 260 participating centres. Based on the success of multicentre collaborative data collection in APRICOT, we have designed a new CTN specifically focused on the neonatal population: NECTARINE **NE***onate* – **C***hildren s***T***udy of* **A***naesthesia p***R***actice* **IN E***urope:* Epidemiology of morbidity and mortality in neonatal anaesthesia: A European prospective multicentre observational study.

The NECTARINE CTN aims to include all neonates and infants from birth to 60 weeks of postmenstrual age undergoing an elective, emergency or urgent diagnostic or surgical procedure, under general anaesthesia with or without regional analgesia or under regional anaesthesia alone. The primary aim of this study is to identify the occurrence of peri-anaesthesia (during and up to the first 120 minutes) interventions needed to treat or improve one of the following: (1) airway management, (2) oxygenation, (3) alveolar ventilation, (4) glycaemia and Na^+, (5) cardiovascular instability, (6) body temperature, (7) brain oxygenation, and (8) anaemia. The parameter or the clinical event that has triggered the intervention will be specifically reported. As secondary aims the in- and out- of hospital morbidity and mortality will be studied at 30 and 90 days from anaesthesia.

Following sample size estimation, based on the preliminary results of APRICOT, we plan to recruit around 5,000 neonates and small infants over a period of twelve consecutive weeks (including weekends and after-hours) across the European countries represented at the ESA Council or part of geographical Europe. Participating hospitals will be provided with data acquisition sheets that enable anonymous standardised recording of all patients' parameters, which will be used by the local coordinator to fill in the electronic case report form (eCRF).

Descriptive statistical analysis will be performed for the primary endpoint, the incidence of medical treatments and/or interventions for critical events during anaesthesia and the corresponding value or clinical condition that has triggered this intervention. Univariate and multivariate analyses will be performed to test factors associated with the endpoints. Results of logistic regression will be reported as adjusted odds ratio (OR) with 95 % confidence intervals.

1.3 List of abbreviations:

ASA score	American Society of Anaesthesiologists 5-category physical status classification system
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CTN	Clinical Trial Network
CTscan	Computed Tomography scan
EC	Ethics Committee
ECMO	ExtraCorporeal Membrane Oxygenation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ESA	European Society of Anaesthesiology
ETT	Endo-Tracheal Tube
FFP	Fresh frozen plasma
GA	General Anaesthesia
GAS	A Multi-site Randomized Controlled Trial Comparing Regional and General Anesthesia for Effects on Neurodevelopmental Outcome and Apnea in Infants
GCP	Good Clinical Practice
GP	General Practitioner
HFOV	High Frequency Oscillatory Ventilation
ICU	Intensive Care Unit
IEC	Institutional Ethical Committee
IRB	Institutional Review Board
MASK	Mayo Anesthesia Safety in Kids study
MRI	Magnetic Resonance Imaging
NIBP	Non-invasive blood pressure
NIRS	Near-infrared spectrometry
OR	Odds Ratio
PACU	Post Anaesthetic Care Unit
PANDA	Pediatric Anesthesia & NeuroDevelopment Assessment Study
PEEP	Positive end expiratory pressure
PICU	Paediatric intensive care unit
PIP	Peak inspiratory pressure
PIN	Patient Identification Number
PMA	Post-Menstrual Age
RBC/PRC	Red blood Cells /Packed red cells
RR	Relative risk
rSO_2	Regional oxygen saturation
SBP/MBP	Systolic blood pressure / diastolic blood pressure
SaO_2/SpO_2	Arterial oxygen saturation / Peripheral oxygen saturation
SOP	Standard Operational Procedure
SGAW	Supraglottic Airways
TIVA	Total intravenous anaesthesia
Vt	Tidal volume

II. INTRODUCTION AND BACKGROUND INFORMATION

2.1 SUMMARY OF FINDINGS FROM NON-CLINICAL STUDIES THAT POTENTIALLY HAVE CLINICAL SIGNIFICANCE AND FROM CLINICAL TRIALS THAT ARE RELEVANT TO THE TRIAL:

Paediatric anaesthesia scientific societies and professional bodies develop and implement clinical practice guidelines in order to standardise paediatric anaesthesia training and service delivery. The overall aim is to improve the quality and safety of clinical paediatric anaesthesia in Europe. Despite advances in knowledge and technology, life-threatening complications can still occur following general and/or regional anaesthesia, and clear predictive factors are not always identified [1-7]. Several single centre cohort studies report the incidence of perioperative anaesthetic complications, but the generalizability of such findings and the prevalence of complications across larger patient populations is not clear [8-9]. Neonates and young infants are at increased risk of perioperative adverse events, that may be associated with prolonged hospital stay, unplanned intensive care admission, and worse outcome [8-9]; all of which can have a considerable impact on the overall quality of life and cost of care.

"APRICOT" was the first prospective multicentre study aimed at establishing the incidence of severe critical events and associated risk factors following anaesthesia in children [ClinicalTrials.gov identifier # NCT01878760]. One of the secondary aims was to establish the mortality rate at 30 days after anaesthesia. This ESA Clinical Trial Network (CTN) project successfully collected data from over 260 participating centres and approximately 30,000 patients, aged from birth to 15 years of age.
While it is expected that APRICOT will provide new information on critical events in children undergoing anaesthesia and 30-day mortality, some limitations can be anticipated with regard to the neonatal population. First, APRICOT will not be able to provide information on the incidence of complications and mortality in neonates who were already mechanically ventilated and transferred to theatre from intensive care, or who underwent surgery directly in the intensive care, as these were exclusion criteria for APRICOT. Secondly, the definition of critical events and the generalizability of the APRICOT findings to the neonatal population are not straightforward. Factors that limit the ability to directly extrapolate data from older children to neonates and infants can be summarised as follows:

1. The range of normal physiological parameters for term and preterm babies under general anaesthesia are not validated: there is still a lack of knowledge on the thresholds for hypo-/hypertension, bradycardia, haemoglobin levels, etc. [10];
2. The need for intervention in case of out-of-range parameters is not clearly defined and there is no clinical evidence yet that a specific clinical or pharmacological intervention may result in a better outcome. For example, there is lack of knowledge on what threshold for low arterial blood pressure may lead to poor outcome [11-12];
3. Pharmacokinetic and pharmacodynamic data for anaesthetic drugs are not completely elucidated in neonates, and dose/response relationships are therefore less predictable than in older children [13];
4. Finally, neonates undergoing general anaesthesia for diagnostic or surgical procedures frequently have multiple co-morbidities (such as extreme prematurity, congenital malformations, congenital heart disease etc.), which may further increase morbidity and mortality [14].

Neonates born at term or preterm, and infants (up to 60 weeks PMA) therefore require additional and specific evaluation, as a separate population from older children. Moreover, neonates and infants are particularly vulnerable patients, with an increased anaesthetic risk [8-9] and higher perioperative morbidity and mortality. Last, the lack of validated and universally accepted "normal" ranges of physiological parameters under general anaesthesia, makes it difficult to develop standardised treatment protocols that aim to minimise negative outcomes.

In addition to the specific issues highlighted above, there is currently increased awareness in the scientific community about the potential neurotoxicity of anaesthetic agents, especially at younger ages [15]. Most of the supporting evidence comes from animal studies, whereas the clinical epidemiological or cohort studies published so far have yielded conflicting results [16-18]. Three prospective projects are currently in progress (GAS, PANDA and MASK) to evaluate potential effects of anaesthetics on the developing brain. However, many perioperative factors, such as physiological instability or type of surgery may both alter anaesthetic management and have a more significant impact on the vulnerable brain of infants. To date, associations between changes in physiological parameters during anaesthesia and early outcome have not been studied in a clinical setting. Indeed, alterations in perioperative physiology (including hypotension, oxygen desaturation, hypoglycaemia, etc.) might be significant factors affecting the early and late outcome (morbidity and mortality).

Further information regarding the safe ranges of perioperative physiological parameters in very young children, and the impact of critical events on postoperative morbidity and mortality is essential to both set up management guidelines and improve outcome. An important first step is to determine what factors trigger an intervention, and which interventions are performed by anaesthetists to correct potentially life threatening conditions. In addition, studying post-anaesthesia morbidity and mortality will provide precious information on populations that are at particular risk of poor outcome.

The occurrence of critical events during anaesthesia management and the need for a specific intervention can be affected by many predicted and unpredicted factors: the clinical condition of the child; the type of surgical procedure; and the overall anaesthesia management. For these reasons it is relevant to collect data from a broad neonatal population undergoing anaesthesia across multiple European Centres undertaking neonatal anaesthesia. Inclusion in the study will not alter the anaesthesia management, and clinical care will continue to be based on anaesthetists' usual practice and local protocols.

The study aims to: (i) identify the type and frequency of treatments used to correct perioperative critical events; (ii) the clinical event and/or threshold of physiological parameters that have triggered an intervention; and (iii) collect data from medical records (or parental questionnaire at 90 days) related to 30 and 90-day morbidity and mortality, in neonates and infants undergoing anaesthesia.

Research questions

1. What is the incidence of significant perioperative medical interventions and/or treatments?

2. What factors have triggered an intervention?
3. Are there specific factors that can predict the need for different forms of intervention?
4. What is the morbidity and mortality at 30 and 90 days after neonatal anaesthesia in Europe?
5. What is the current routine clinical practice of neonatal anaesthesia in Europe?

2.2 COMPLIANCE OF STUDY WITH THE PROTOCOL, GCP AND THE APPLICABLE REGULATORY REQUIREMENT(S):

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Ethics Committee (EC) as appropriate to local regulatory requirements in participating centres, and according to Good Clinical Practice standards. No substantial Amendment to the protocol will be implemented without the prior review and approval of the IRB/EC. However it is unlikely that major protocol changes will be required for this observational study. There is no requirement to notify the main IRB/EC of Administrative changes or non-substantial amendments, but sponsors or chief investigators wishing to do so voluntarily should use a separate covering letter. The letter should make it clear that the amendment is not substantial and does not require an ethical opinion.

Particular regulatory requirements of specific countries will be followed.

2.3 STUDY POPULATION:

The study population will include all neonates and infants from birth to 60 weeks of post-menstrual age (PMA), scheduled for an elective, emergency or urgent diagnostic or surgical procedure, (both cardiac and non-cardiac), under general anaesthesia with or without regional analgesia, or under regional anaesthesia alone.

III. TRIAL OBJECTIVES AND PURPOSE

Primary objective:

To determine the incidence of peri-anaesthetic intervention(s) and/or medical treatment(s) performed in response to a potentially life-threatening critical event or to correct major deviations in physiological parameters.

Secondary objectives:

a) To investigate the occurrence of adverse events in the immediate postoperative period (up to 120 minutes after anaesthesia), and evaluate links with intraoperative critical events.
b) To investigate predictive factors for life-threatening critical events.

c) To investigate potential predictive factors for significant deviations in physiological parameters.
d) To determine mortality within 30 days after anaesthesia.
e) To determine morbidity at 30 days after anaesthesia (if still in hospital), or until hospital discharge, based on the medical record
f) To report mortality at 90 days after anaesthesia via hospital records or parental questionnaire.
g) To evaluate associations between critical events and increased morbidity and mortality.
h) To describe the differences in neonatal anaesthesia practice throughout Europe.

IV. STUDY DESIGN

4.1 STUDY DESIGN, PRIMARY AND SECONDARY ENDPOINTS:

Study design:

Prospective, observational, multi–centre cohort study.

Primary endpoint:

The incidence of **interventions** performed by the anaesthesia team in response to (i) a critical event or (ii) a major change of physiological parameters during anaesthesia management.

List of physiological parameters that will be observed for (i) and (ii):

1. Airway management
2. Peripheral oxygen saturation (SpO_2) and/or arterial oxygen saturation (SaO_2) ;
3. End-tidal carbon dioxide (CO_2) (and/or arterial or venous CO_2);
4. Glycaemia, and Na^+;
5. Cardiovascular instability: blood pressure, heart rate;
6. Body temperature;
7. Brain oxygenation by NIRS (if available);
8. Haemoglobin level.

Secondary endpoints:

- The incidence of adverse events up to the first 120 minutes after anaesthesia.
    - Post-anaesthesia events to be reported are:
        - Unplanned PICU/NICU admission.
        - Unplanned delayed extubation.
        - Need for ECMO.
        - Need for chest left open (for cardiac surgery only).
        - Unplanned hospital admission (originally scheduled as outpatient).
- In-hospital mortality up to 30 days after anaesthesia as determined from medical records.
- Morbidity at 30 days after anaesthesia as determined from medical records: until discharge or at 30 days if still in hospital.
- In- and out-hospital mortality and morbidity at 90 days after anaesthesia.

For definitions of these peri-anaesthesia interventions and the instructions for data collection, please refer to section IX.

4.2 DATA COLLECTION:

General instructions for data storing

Data will be collected in individual centres on paper case report forms (CRFs). Paper and electronic CRFs will be in English for all Nations and centres involved in this trial. Paper CRFs will be stored within a locked cabinet/office in accordance with local and national regulations. Paper (primary) CRFs will have an identifiable patient data page in order to allow follow-up of clinical outcomes and data possibly monitoring visits by national coordinators or regulatory committees. These data will be transcribed by local investigators onto an internet based electronic CRF and assigned an anonymised code. No patient identifiable data will be directly accessible from the electronic CRF.

A photocopy of the original anaesthetic medical record will be stored in a locked cabinet/office, separated from the paper CRFs, to confirm the existence of individual patients and to retrieve missing or incorrect data reported in the paper and electronic CRFs.

Each Nation and Centre will be identified by a numeric code, and each patient will be assigned an additional numeric code. This will allow local investigators to identify individual patients, but the coordinating team will have access only to anonymised data. All electronic data transfer between participating centres and the coordinating centre will be username and password protected. Each centre will keep a trial file, which will include a copy of the protocol, local investigator delegation log and proof of ethics approval. A list of participants (patients) will be available in each centre to match identified codes in the database with individual patients in order to record clinical outcomes, supply missing data points, and facilitate local follow-up of primary and secondary outcomes.

The following data will be collected for each patient:

I. Inclusion criteria & Identifying data (to be handled separately – not transferred to eCRF):

1. Screening, with inclusion criteria
    a. Corrected age calculation: only children aged less than 60 weeks of corrected age will be included in the study. The corrected age will be calculated as following: baby's age at birth since last mother menses (gestational age) in weeks plus baby's age at anaesthesia in weeks. If corrected age is less or equal to 60, then the child can be included in the study.
2. Identifying data
    a. Date paper CRF created
    b. Date of birth
    c. Identification data (to be filled in with available data, and only for local follow-up use): Child's first name and last name, Family address, phone numbers and email contact, Child's paediatrician or family doctor (with details of contact, included email), and telephone number for the 90 day follow-up. Only an anonymous patient identifier (study subject ID) will be transferred to the electronic CRF.

CRF1: Preoperative

I. Patient information & consent & medical history

1. Subject ID: is formed by 9 digit codes: 3 for country, 3 for centre, 3 for each patient. Multiple anaesthesia in the same patient will be identified with the same patient's 9 code.
2. If parental consent is required by local regulatory requirements, plus the date of parental consent signed by one or both parents should be recorded.
3. Gestational age at birth (weeks).
4. Birth weight (kg).
5. Gender.
6. Maternal medications and health issues during pregnancy, with specification of disease or drug use (if data available).
7. Mode of delivery: vaginal delivery or caesarean section.
8. Apgar score at 1 minute (if available).
9. Apgar score at 5 minutes (if available).
10. Child's known congenital or chromosomal abnormalities.

CRF2: Anaesthesia Data

I. Medical History

1. History of previous apnoea and/or respiratory support.
2. History of intraventricular haemorrhage and grade (from 1 to 4).
3. History of previous ECMO support.
4. History of PDA (patent ductus arteriosus) and it was no treated, treated medically or surgically.
5. History of previous surgery, number and of current surgery is planned for a complication or incomplete previous surgery.

II. Current medical condition (the day of anaesthesia)

1. Study subject ID (9 code).
2. Subject multiple anaesthesia: 01 if first anaesthesia during the Nectarine Study, 02 second, 03 third, etc. in case of multiple anaesthesia.
3. Child's age (in weeks and days)
4. Child's weight (in kg)
5. Location child admitted from.
6. Child's breathing condition prior to anaesthesia: no oxygen, or ventilator support, child on oxygen, under NIV, intubated on conventional ventilation, intubated on non-conventional ventilation (HFOV), on ECMO.
    a. If child is already intubated (ETT), the primary reason for intubation (clinically instable or for surgery) will be indicated.
7. Place where the procedure is performed
8. Current medications at the time of anaesthesia including sedatives, opioids, muscle relaxants, and vasopressors or inotropes (antibiotics excluded).

III. Medical assessment of the child on the day of anaesthesia

1. Current respiratory problems, and if yes, available details.
2. Current cardiovascular problems, and if yes, available details.
3. Current metabolic problems, and if yes, available details.
4. Current neurological/brain problems, and if yes, available details..
5. Current renal problems, and if yes, available details..
6. ASA score (from I to V). ASA I is applicable if child > 3 months of age.

IV. Baseline Physiological and Metabolic parameters

1. For physiological parameters, include values the anaesthesiologist in charge considers as baseline. This may be parameters taken: i) from the medical record (within the 24 hours), ii) before induction, or iii) the first measurement after induction of anaesthesia. Baseline physiological parameters can include: systolic blood pressure, mean blood pressure, diastolic blood pressure, heart rate, SpO_2, (note if pre-ductal and/or post-ductal values) SpO_2, body temperature, and NIRS if used.
2. Metabolic parameters: Na^+, Hb, glucose.

V. Indication for surgery or non-surgical procedure and Anaesthesia management:

1. Date and time of anaesthesia (induction).
2. Date and time of surgery/procedure start (knife to skin or patients hands on).
3. Degree of urgency: elective, semi-elective/urgent or emergent surgery. For definitions of degree of urgency, refer to the End of study report section.
4. Indication: surgical or non-surgical procedure. If surgical, specification of minimally invasive (laparoscopy, thoracoscopy, etc.) is requested, and if surgery was concluded as minimally invasive or converted to open surgery. The principal surgery (if more than one) will be indicated.
5. Anaesthesia team involved, with specification of number of staff in charge of the patient.
6. Monitoring applied.
7. Anaesthesia technique of choice: general anaesthesia, regional anaesthesia alone, or combined general and regional anaesthesia.

V-1. General anaesthesia:

1. Type of anaesthesia induction (first route of administration: inhalational, intravenous, or intramuscular), and specification of drug (s) used for induction (anaesthetic agents) and opioids.
2. Neuromuscular block agent used and time of administration (if prior or after intubation), and if reversal was administered at the end of anaesthesia.
3. If drug(s) for maintenance were given, specify anaesthetic(s) and opioid(s).
4. Carrier gas used for anaesthesia: oxygen, oxygen and N_2O, oxygen and air, air, other
5. If vasopressor or inotropic infusion was commenced as part of routine anaesthesia practice from the beginning

V-2 Regional anaesthesia: specify type of block used, and if a catheter was inserted for continuous analgesia.

VI. Airway management

1. Specific equipment used for airway management (face mask, supraglottic airway, endotracheal tube, tracheostomy, nasal probe, CPAP/non-invasive ventilation, non-invasive, none).
2. And if ETT: type of tube used (cuffed or uncuffed).
3. Route of ETT insertion: oral or nasal.
4. Cormack-Lehane score, if known.

VII. Ventilation:

1. Type of initial ventilation: spontaneous, assisted ventilation, controlled ventilation (volume controlled, pressure controlled, pressure regulated volume controlled, HFOV, other), and the initial setting for controlled ventilation (PIP, PEEP and FiO_2).

VIII. Details of timing:

1. Specify the date and time of end of surgery/procedure and end of anaesthesia

IX. Recording of "interventions" occurring during anaesthesia, and the immediate post-anaesthesia care (up to 120 minutes after the end of anaesthesia, or until the child is discharged from recovery room or PACU). This data is essential for answering the primary end-point.

Definition of "intervention": an action/medical treatment performed in response to a critical event and/or a physiological parameter derangement as judged by the anaesthesia team. The medical treatment given for preventing a critical event will not be considered as an intervention. **The intervention/medical treatment performed MUST always be accompanied by the parameter or condition that has triggered the intervention and both data will be reported.**

1. **Interventions for airway management.** It is defined as more than 2 attempts of intubation, which require alternative strategies for achieving successful intubation.
   Interventions can be:
   a. alternatives to traditional laryngoscopy: change of laryngoscope blades, assisted fiberoptic intubation, video–assisted intubation, use of air-track, use of stylet or bougie, emergency tracheostomy, supraglottic airway device, call for help on an ENT colleague or 2nd senior anaesthesiologist, blinded intubation and other.
   b. If the difficult intubation was an unexpected occurrence.
   c. If difficult intubation was associated with difficult face-mask ventilation.
   d. If difficult intubation was associated with drop in oxygenation.
   e. If difficult intubation was associated with bradycardia.
   f. Number of attempts until successful intubation was achieved.
   g. Outcome of the event: successful intubation; unsuccessful intubation but procedure was performed under facial or laryngeal mask ventilation; impossible intubation and patient woken up from anaesthesia and procedure postponed.

2. **Oxygenation: Interventions for hypoxaemia.** Oxygenation will be monitored via the peripheral oxygen saturation (SpO_2) with the pulse oximeter positioned whenever possible on the right hand (pre-ductal), and/or with measurement of oxygen arterial pressure (PaO_2). Interventions for low oxygenation are defined as any action or pharmacological treatment performed by the anaesthesia team and aimed at improving oxygenation. The corresponding lowest SpO_2 and/or PaO_2 value that has triggered this intervention will be reported.
   Interventions for improving oxygenation (tick all that are applicable):
   - Emergency/unplanned intubation (only if patient previously not intubated).
   - Change or repositioning of an accidental dislocated or obstructed tube.
   - Need for FiO2 higher than for routine practice (or persistent need of FiO_2=1).
   - Need for PEEP higher than for routine practice.

- Need for prolonged manual ventilation in already intubated/ventilated patient.
- Recruiting manoeuvre(s).
- Switch from conventional to non-conventional ventilation (HFOV).
- Drainage of an acute pneumothorax.
- Pharmacological treatment of laryngospasm.
- Pharmacological treatment of bronchospasm.
- Other (specify).

Time of occurrence of hypoxaemia, number of intra-anaesthesia episodes, the SpO_2 and/or PaO_2 that has triggered the intervention, the duration of the episode(s), the outcome (successful improved oxygenation, persistent hypoxemia, or deterioration of oxygenation despite intervention performed) will be reported.
If the poor oxygenation was accompanied by a drop in rSO_2 by NIRS monitoring, the corresponding section VII (brain oxygenation) will be filled in.
Finally, whether poor oxygenation was associated with difficulty with ventilation and hypercapnia should be reported at the end of this section.

3. **Intervention for <u>HYPO or HYPERcapnia without associated hypoxaemia.</u>** End-tidal (Et) and/or arterial/venous carbon dioxide (CO_2) is part of routine anaesthesia care (except if regional anaesthesia is used alone) and is maintained within a normal range by alveolar ventilation. Intervention for improving alveolar ventilation is defined as an action performed by the anaesthesia team aimed at correcting abnormal CO_2 levels. The corresponding value ($EtCO_2$ and/or blood CO_2) that has triggered this intervention will be reported.

   a) **<u>Interventions for improving alveolar ventilation</u>** (tick all that are applicable):
      - Change of ventilation modality.
      - Change of airway device/management (from face mask/SGAW to ETT).
      - Change of the equipment dead-space.
      - Need for Peak Inspiratory Pressure higher than for routine practice
      - Prolonged/persistent manual ventilation.
      - Alveolar recruitment manoeuvre.
      - Other (specify).

Time of occurrence of hyper/hypoCO_2, number of intra-anaesthesia episodes, the EtO_2 and/or $PaCO_2$ has triggered the intervention, the duration of the episode(s), the outcome (successful/improvement, persistent difficult ventilation) will be reported.
If the high/low CO_2 was accompanied by a drop in rSO_2 by NIRS monitoring, the corresponding section VII (brain oxygenation) will be filled.

4. **Interventions for correcting blood <u>glucose, Na^+ levels</u> (defined as metabolic intervention)**. Intervention for high/low glucose and/or Na^+ is defined as a treatment performed by the anaesthesia team aimed at correcting abnormal levels of the above mentioned parameters. The lowest/highest values that triggered the intervention will be

reported.

a) Intervention for high/low glucose:
    - Administration of i.v. glucose (bolus or continuous infusion).
    - Stop i.v. glucose or fluids containing glucose.
    - Onset of insulin treatment.
b) Intervention(s) for high/low Na^+:
    - Administration of additional Na^+.
    - Stop of i.v. glucose or hypotonic solutions.

The blood glucose and/or Na^+ level that triggered the intervention will be reported, with the outcome after treatment (successful/parameter corrected, or persistent disorder).

5. **Intervention for <u>cardiovascular instability.</u>** It is defined as an intervention and/or a medical treatment to control a state of cardio-vascular instability. This clinical condition can be triggered by the occurrence of hypotension or hypertension, and/or cardiac rhythm disturbances on the ECG. Data reported will include the intervention made and the critical event or value for heart rate (zero if cardiac arrest) and/or blood pressure (with specification if systolic, mean or diastolic blood pressure) that triggered the intervention.
    a) Intervention for blood pressure (specification if systolic, mean or diastolic blood pressure and the corresponding value):
        - Bolus of more than 20 ml/kg crystalloid fluid (also 2 x 10 ml/kg) above routine maintenance infusion.
        - Bolus of 10 ml/kg or more of albumin and/or colloids.
        - Administration of fresh frozen plasma (FFP) for hypovolemia leading to CV instability.
        - Administration of packed red cells (PRC) (in this case indicate if Hb, blood pressure or ongoing bleeding was the primary reason for transfusion and the appropriate value).
        - Administration of vasoactive drug bolus or infusion (ephedrine, phenylephrine, noradrenaline/norepinephrine, dopamine, dobutamine, epinephrine/adrenaline, milrinone, levosimendan, nitroprusside).
    b) Intervention for ECG disturbance:
        - Atropine or glycopyrolate administration (not given to prevent but only for treatment).
        - Administration of epinephrine, Ca, Mg.
        - Administration of lidocaine i.v.
        - Administration of amiodarone i.v.
        - Electric defibrillation.
        - External pacing.
        - Chest compression < 1 minute.
        - Cardiopulmonary resuscitation (CPR).
        - Other (specify).

Time of occurrence of haemodynamic instability or ECG disturbance, number of intra-anaesthesia episodes, the blood pressure and/or heart rate that triggered the intervention, the

duration of the episode(s), the outcome (successful/improvement, persistent instability) will be reported.
If the high/low blood pressure or ECG disturbance were accompanied by a drop in rSO2 by NIRS monitoring, the corresponding section VII (brain oxygenation) will be filled.

6. **Intervention for correcting body temperature.** Whenever body temperature (oesophageal, rectal or cutaneous) is part of routine monitoring, intervention for derangements in body temperature and the value that has triggered the intervention will be reported.

   Interventions for core body temperature derangement, in both directions (hypo/hyper):

   - New onset of warming fluids (if not already in use).
   - Active warming with blankets (if not already in use).
   - Cooling fluids.
   - Cooling body.
   - Other (specify).

Body temperature that triggered the intervention, the outcome (successful/improvement) and associated complications (cardiovascular instability, coagulopathy) will be reported.

7. **Interventions induced by poor Brain oxygenation.** Whenever brain oxygenation with NIRS monitoring is part of routine care, the occurrence of low rSO2 will be reported, with the corresponding lowest value, and the clinical condition that has caused the low brain oxygenation, based on the judgment of the anaesthesia team. If an action and/or a medical treatment applied by the anaesthesia team in response to derangement of a physiological parameter, or a critical condition is accompanied and/or triggered be a low rSO2, this section also needs to be completed. This is aimed at better understanding the "physiological" from the "operational" ranges of normality and the level of inter-individual variability [10].

   Interventions for low rSO2:

   - none.
   - Alteration in ventilation.
   - Intervention for blood pressure.
   - Intervention for oxygenation.
   - Intervention for haemoglobin.
   - Intervention for cardiac output (inotropes or via CPB in cardiac surgery).
   - Other (specify).

8. **Packed Red Cells (PRC) administration for acute anaemia.** If PRC were given for new onset of intraoperative anaemia, and not for cardiovascular instability as the primary reason, the Hb level that triggered the intervention and the volume administered will be reported.

X. Immediate post-anaesthesia outcome. End-of-anaesthesia and Recovery Room (or PACU) data collection. These data will be collected until Recovery room discharge or up to 120 minutes if still in Recovery Room.

- Where the patient was transferred after anaesthesia: PICU/NICU, Intermediate care/High dependency unit, ward.
- If patient was transferred to PICU/NICU, specification if ICU admission was unplanned, and related to one or more above reported critical events, and the status of ventilation at ICU admission
- If still intubated, specify if delayed extubation was unplanned.
- Postoperative bleeding (need for surgical revision).
- Need for ECMO.
- Need for chest to be left open (only for cardiac surgery).
- Unplanned hospital admission, if scheduled as outpatient.

CRF3: Data collection for post-anaesthesia morbidity and mortality. 30-day morbidity and mortality (this part is mandatory for ALL included patients).

Data should be collected at 30 days after LAST anaesthesia through the medical record, and will capture information until hospital discharge or at 30 days if patient is still in hospital. ALL questions should be answered if patient is "Dead", "Discharged before day 30", "Still in hospital at day 30". If patient status is "Follow-up not performed/not available" all the questions will be left empty. In case of multiple anaesthesia occurrences, this section will be completed 30 days after LAST anaesthesia.

The following data will be collected:

- Date of follow-up
- Patient status on the day of follow-up: discharged home, discharged to another hospital, still in hospital, still in ICU, death.
- If dead or discharged, the day of death/discharge and if death and the specification of the suspected primary cause of death will be requested

CRF3-A: Morbidities at 30 days. Complications occurred after anaesthesia and until the day-30 will be reported as follow:

- Any ICU admission/re-admission after the immediate postoperative period, the total days in PICU/NICU (zero if never), and the total days of ventilation (zero if never ventilated).
- Brain/CNS: intracranial bleeding and/or ischaemia (MRI/CT and/or US documented), occurrence of seizures (clinically or EEG documented), new onset of hypotonia or hypertonia.
- Surgical morbidities: severe surgical site infection requiring new onset of antibiotics, re-surgery due to unsuccessful or complicated first surgical treatment, need for prolonged parenteral nutrition due to surgical complication. .
- Respiratory:, failure of weaning from ventilation (and/or tracheal extubation failure) with prolonged ventilatory support, need for re-intubation, pneumothorax, pleural effusion, pneumonia, ECMO.

- Cardio-vascular: arrhythmia, episode(s) of cardiac arrest, cardiac ischemia (elevation of troponine), arteria/venous embolism, ECMO, venous thrombosis, inotropes or vasopressors.
- Liver failure: coagulation disorders (defined as INR>2), increase in serum bilirubin (>300 micromol/L; >10 mg/dL).
- Renal insufficiency: peritoneal dialysis, increase in creatinine levels necessitating adaptation of the medical treatment or CRRT (continuous renal replacement therapy).

CRF3-B: 90-day mortality (this part is mandatory for ALL patients)

Data should be collected 90 days after anaesthesia and they will include in- and out-of-hospital mortality. ALL questions should be answered if patient is'Alive' or "Dead". If 'Alive' state if "Discharged between day 30 and 90", "Still in hospital at day 90". If patient status is "Follow-up not performed/not available" all the questions will be left empty

- Date of discharge/death and the suspected cause of death (if death) will be reported.
- Hospital re-admission after the child was discharged will be reported with the principal reason for readmission.

Telephone interview with parents (or caregivers, or paediatrician/general practitioner): this telephone call will be performed 90 days after the last anaesthesia, if the child was discharged from hospital, or during a face-to-face if still in hospital. If the patient is still in hospital, data can be collected from its medical record. General instructions for telephone call are summarised in appendix 5 'Telephone call for 90-day follow-up' and can be translated and approved in different languages, if required.

XI. End of study report

At the end of the study period each centre will provide an "end of study reporting form" (see appendix #6) containing the total number of the anaesthesia procedures performed under anaesthetic care during the study period and the number of patients included in the study, as well as the cause(s)of failure to record some records, if any.

The following **definitions** of General Anaesthesia (from the American Society of Anaesthesiologists - ASA) and elective, semi-elective, urgent and emergency surgical procedure will be used in the NECTARINE study.

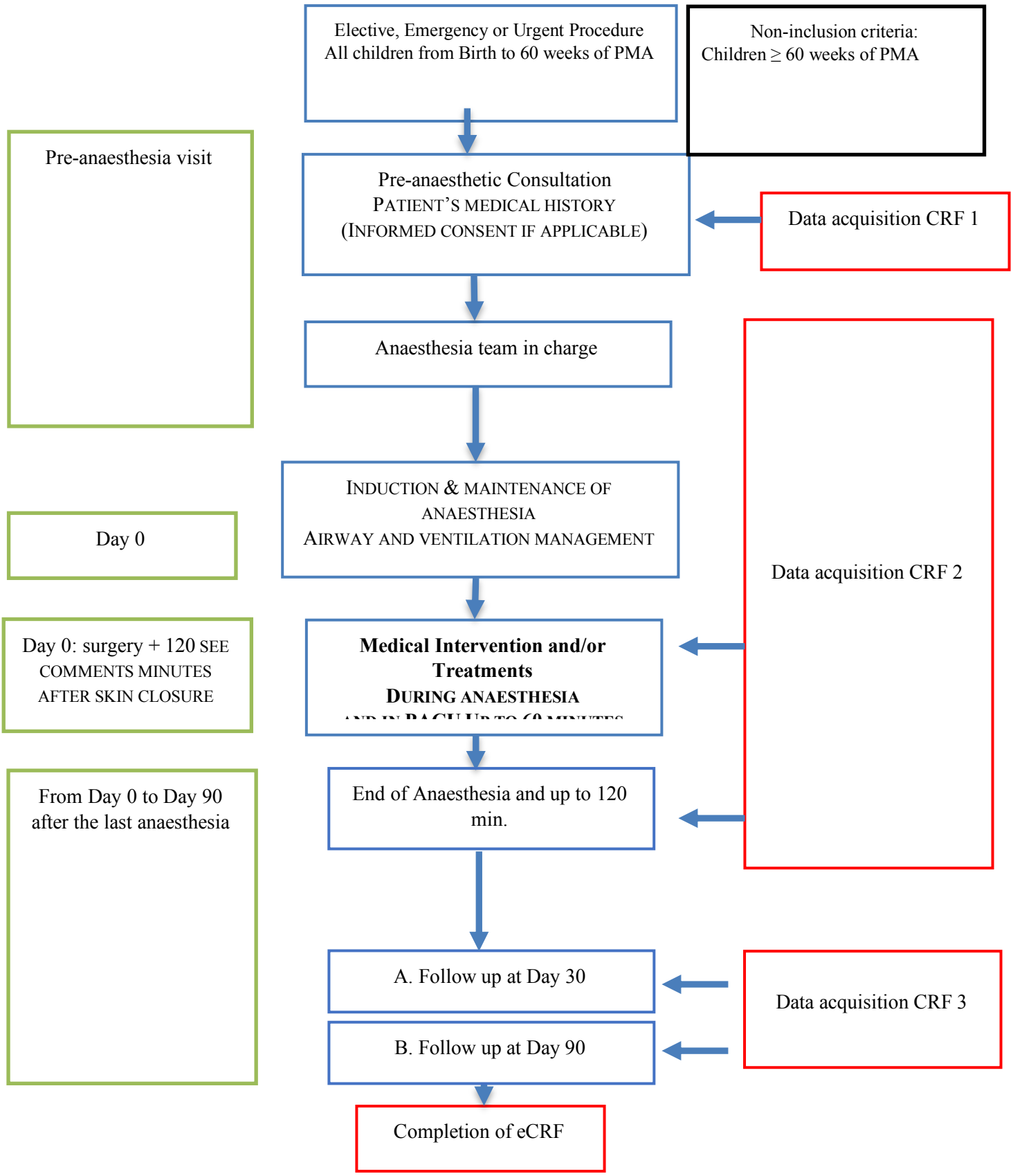
- General anaesthesia: A drug-induced loss of consciousness during which the patient is not arousable, even to painful stimuli. The ability to maintain independent ventilatory function is often impaired. Assistance is often required in maintaining a patent airway. Positive pressure ventilation may be required due to depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.
- Definition of elective procedure: When a procedure is scheduled in advance and does not involve any medical emergency/urgency, it is an elective procedure.

- Definition of semi-elective procedure: is a surgery that must be done to preserve the patient's life, but does not need to be performed immediately. It is frequently scheduled few days in advance.
- Definition of emergency procedure: non-elective procedure performed when the patient's life or well-being is in direct jeopardy.
- Definition of urgent procedure: procedure required within less than 48 hours.

4.3 Type/design of trial:

NECTARINE is a prospective, observational, multi–centre cohort study. It only includes objective data collected as part of routine anaesthetic care. As a consequence NECTARINE has to be referred as an observational trial, where no intervention other than justified by clinical judgment takes place. Therefore this study is neither double-blind, nor placebo-controlled. Apart from standardised data acquisition, **there will be no alteration to usual patient** care. An outline of the trial design is given in the protocol flow chart below.

4.4 Protocol Flowchart: Schematic Diagram Of Trial Design, Procedures And Stages:



4.5 DESCRIPTION OF THE MEASURES TAKEN TO MINIMIZE/AVOID BIAS:

The NECTARINE study is a prospective observational cohort study that includes data collection, but does not alter or influence routine care. In order to avoid a potential bias, all, or as many as possible, patients younger than 60 weeks of PMA need to be included in each participating centre. The patient's clinical care will not be modified by study participation (observational study). All centrally collected data will be anonymized and collected on a secure website: therefore there is high probability that written parental approval to participate will be waived by the local IRB even though approval for a phone call at 90 days follow up will be asked. (See ethics section)

In order to ensure adequacy and accuracy of data collection, national and local co-ordinators will be appointed with the following responsibilities:

National co-ordinators:

National co-ordinators will be appointed by the Steering Committee to lead the project within individual nations and:

- Identify local co-ordinators in participating hospitals
- Assist with translation of study paperwork as required
- Ensure necessary country or regional regulatory approvals are in place prior to the start date
- Assist and train the local co-ordinator and monitor conduction of study according to good clinical practice
- Help co-ordinating flow of information and data cleaning in his/her country

Local co-ordinators:

Local co-ordinators in individual institutions will:

- Provide leadership for the study in their institution
- Ensure all relevant regulatory approvals are in place for their institution
- Ensure adequate training of all relevant staff prior to data collection
- Supervise daily data collection and assist with problem solving
- Act as guarantor for the integrity and quality of data collected
- Ensure timely completion of eCRFs and follow-up
- Communicate with the relevant national co-ordinator

4.6 EXPECTED DURATION OF SUBJECT PARTICIPATION AND DESCRIPTION OF THE SEQUENCE AND DURATION OF TRIAL PERIODS:

Each patient included into the NECTARINE study will be followed up during the anaesthesia management and until discharge from the recovery room or the PACU (or up to 120 minutes after

the end of anaesthesia, if they remain longer in the recovery room or PACU). Furthermore, patients will be followed up at 30 days after anaesthesia for incidence of morbidities and mortality.

Multiple anaesthesia: if a patient undergoes a further anaesthetic during the recruitment period, and he/she still meets the inclusion criteria for NECTARINE, then the follow-up for morbidity and mortality will be performed 30 days after the LAST anaesthesia. This will include morbidity and mortality from the end of the first anaesthesia to the date of follow-up.

Parents of the patients will also be asked if they agree to be contacted by telephone 90 days after anaesthesia with the aim of capturing any additional mortality and morbidity, in- and out-of-hospital. The 90 days will be calculated with the same criteria as the 30-day follow-up: 90 days after the LAST anaesthesia.

4.7 "STOPPING RULES" OR "DISCONTINUATION CRITERIA" FOR INDIVIDUAL SUBJECTS, PARTS OF TRIAL AND ENTIRE TRIAL:

Apart from withdrawal of consent no specific "stopping rules" or "discontinuation criteria" exist.

V. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 SUBJECT INCLUSION CRITERIA:

Patients from birth to 60 weeks of PMA admitted to participating centres during the 12-week recruitment period for:

- Any inpatient or outpatient procedure under general anaesthesia with or without regional analgesia or under regional anaesthesia alone in the operating theatre. This includes all kinds of surgeries (both cardiac and non-cardiac) along with non-surgical procedures requiring anaesthesia and analgesia to be performed such as central venous access, burn care, cast, etc.,

- any diagnostic procedure under the care of the anaesthesia team (such as endoscopy, radiology (CT-scan, MRI), cardiac catheterisation and electrophysiology, PET-scan, radiotherapy, lumbar and bone marrow puncture, biopsies) performed at out-of-operating room locations,

- Any diagnostic or surgical procedure under general anaesthesia performed by the Anaesthesia Team in Neonatal or Paediatric Intensive Care Units.

The corrected age (or PMA) will be calculated as follow: Baby's age at birth since last mother's menses (gestational age) + Baby's age in number of weeks since birth. For example: the child was

born at 30 weeks, and the current age is 15 weeks, the corrected age is 30 + 15 = 45. This child is eligible for the Nectarine.

5.2 SUBJECT EXCLUSION CRITERIA:

- All children aged ≥ 61 weeks PMA.

5.3 SUBJECT WITHDRAWAL CRITERIA:

Apart from withdrawal of consent subjects will not be withdrawn from the trial.

In case of withdrawal of consent, data collection will be stopped and the case report form (CRF) and the electronic case report form (eCRF) of this patient will be left empty or deleted if already started. In case of withdrawal of consent subjects will not be replaced. Subjects that have withdrawn consent will not be followed-up.

5.4 MULTIPLE PROCEDURES: see 4.6.

VI. STATISTICAL ANALYSIS

6.1 SAMPLE SIZE:

The primary end-point of the NECTARINE study is to evaluate the incidence of medical interventions for life threatening conditions or critical events (as reported in section IX) in neonates and infants (aged between 0-60 weeks of PMA) who had undergone general and/or regional anaesthesia.

A secondary aim of the study is to identify the potential predictors of critical events and poor outcomes (morbidity and mortality); since this requires a minimum number of events to be observed, this number has been estimated first as described below.

A total of **5,000** patients are expected to be enrolled in the present study based on the fact that a minimum number of **462** events is required in order to analyse the data through multivariate regression analysis models for the identification of the potential predictors of poor outcomes.

In fact, the number of **462** patients was obtained considering the following:

- According to the formulation n. 2 cited in Hsieh (1998), that allows for the calculation of the minimum sample needed for a logistic regression analysis with only 1 covariate, a minimum number of 776 patients (388 cases + 388 controls) is

required assuming that: P1=0.4 [P1=pr(diseased|X=0)], P2=0.5 [P2=pr(diseased|X=1)], B=0.5 (B=the proportion of the sample with X=1), alpha=0.05 (alpha=Type 1 error), and power=0.80 (power=power for testing if the Odds Ratio is equal to one). This calculation was performed with the software "R", release 3.1.3 (The R foundation for Statistical Computing) using the function "SSizeLogisticBin".

- According to the same author Hsieh (1998), the previous number of 776 patients had to be corrected in order to take into account the fact that there would be more than 1 covariate in the model. The correction consisted of multiplying the previously obtained number of 776 by the Variance Inflation Factor [VIF= $1/(1-rho^2)$], where rho^2 is the multiple Correlation Coefficient relating X_1 with $X_2,\ldots.X_p$. Assuming that rho is equal to 0.4, a total number of **924** patients will be required for the "fitting" of the multivariate logistic regression models (corresponding to **462** cases + 462 controls).
- Considering that the expected percentage of events is approximately 11%, **4,200** patients are the minimum required in order to obtain 462 cases. However, taking a drop-out rate of 15% (p_{DO}=0.15), into account, **4,941** patients is the exact number required for the study, obtained with the following formula: $N_{DO}=N/(1-p_{DO})$ and, in sensibly rounding up this figure, we arrive at **5,000**.
- The estimate of the expected percentage of events was approximately 11%. This estimate was based on preliminary results from the "APRICOT" study whose data is still under analysis. Such data though, due to its confidential nature, is not given herein but can be provided to the local Ethical Committee if needed.

It should be noted that the 462 controls will be randomly selected from the remaining non-cases of the initial cohort and included in the multivariate logistic regression analysis.

A scenario with different expected percentages of events is illustrated in the following table:

Patients needed to be enrolled	**Expected percentages of events**	**Number of events to be observed (deaths or critical events)**
4,200	12%	504
4,200	11%	462

4,200	10%	420
5,000	12%	600
5,000	11%	550
5,000	10%	500

6.2 STATISTICS:

Descriptive analysis of the entire cohort of patients will be performed first. Patients characteristics will be provided with categorical data summarised in terms of absolute frequencies and percentages, quantitative variables summarised in terms of means and Standard Deviations (SD) in the case of normally distributed data and in terms of medians with 1st and 3rd quartiles (1st – 3rd q), or minimum and maximum values (Min-max) in the case of skewed distributed data. The normality of the distributions will be evaluated by the Shapiro-Wilk test.

The occurrence of the primary end-point (number of deaths or critical events) will be reported as a frequency and 95% Binomial Exact Confidence Intervals will be provided.

A detailed description of the observed critical events will also be given. In addition, the associations between categorical data will be evaluated by the Chi-square test or by the Fisher's Exact test in the case of expected frequencies less than 5. The relationship between quantitative variables and the outcome (poor outcome: yes/no) will be evaluated by the Student's *t* test or the Mann-Whitney U test in the case of skewed distributed variables or homoschedasticity assumption not being fulfilled. The relationships between quantitative variables and categorical polynomial variables will be evaluated by the Analysis of Variance (F test), or by the non-parametric analysis of variance (Kruskal-Wallis test). In order to avoid the "multiple comparison error", the Scheffé test will be used as *a posterior* test or the Bonferroni's correction will be applied. In the latter case, the P value will be reported as "P_B".

All the tests will be two-sided and a P value < 0.05 will be considered as "statistically significant".

Finally, a logistic regression model will be fitted in order to identify the potential predictors of poor outcome. Variables that were statistically associated with the outcome at the bivariate analysis or clinically relevant variables will be entered into the model. The log-Likelihood Ratio (LR) test will be used to test the relevance of each variable in the model. Adjusted OR (OR_{Adj}) with 95% Confidence Intervals (95% CI) will also be calculated and reported.

The Area Under ROC Curve of the model will be used as a measure of the goodness-of-fit of the model.

The software "Statistica", release 9 (StatSoft Inc., Tulsa, OK, USA) will be used for all univariate and bivariate analyses and the software "Stata", release 11.0 (StataCorp, College Station, TX, USA) will be used for all the multivariate analyses. [29]

6.3 CENTRES:

NECTARINE study will recruit as many participating institutions (private or public, academic, regional or referral centre) as possible across the European countries represented at the ESA Council and physical Europe. The recruitment will take place over a period of twelve consecutive weeks on a 24/7 base. The 12-week recruitment period will be commenced in the course of 2016. .

Each centre will have a local co-ordinator and a national co-ordinator will be in contact with the participating centres in his/her country to ensure all clarification and follow recruitment. For detailed responsibilities, please refer to the section 4.5 above and ESA SOPs.

6.4 METHODS:

NECTARINE is a descriptive study; descriptive statistical methods will be used for the primary endpoint: the occurrence and 95% confidence interval will be given. The data to be collected during the actual patient study are all part of routine clinical care. Since the NECTARINE study is a descriptive trial, and no changes of routine care are associated with the study no interim analysis is planned.

6.5 THE LEVEL OF SIGNIFICANCE TO BE USED:

A significance level of $p<0.05$ will be used for all statistical analyses.

6.6 CRITERIA FOR THE TERMINATION OF THE TRIAL:

Since no intervention will be performed there are no criteria for termination of the trial.

6.7 PROCEDURE FOR ACCOUNTING FOR MISSING, UNUSED, AND SPURIOUS DATA:

All patients will enter data analysis, regardless whether all data of the CRF has been surveied. Unused and spurious data will be excluded from data analysis as soon as it is recognised.

6.8 THE SELECTION OF SUBJECTS TO BE INCLUDED IN THE ANALYSES:

All subjects that are included in the study will be included in the data analyses.

VII. QUALITY ASSURANCE AND QUALITY CONTROL

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. There will be monitoring of the eCRF data by the ESA staff, but no monitoring of source data by ESA. Possibly monitoring visits by national coordinators or regulatory committees will be sent to local sites to review the source documents for this observational study.

Agreements, made by the sponsor with the Chief Investigator, should be in writing, as part of the protocol or in a separate agreement.

The Sponsor has not put in place any form of contract or agreement with sites to cover the activities they will undertake for the study. This is a very low risk data collection study and no harm will arise to patients as no aspect of their normal clinical care is being affected. Any issues with the treatment they receive within the hospital they attend will be covered by local indemnity.

VIII. ETHICS DESCRIPTION OF ETHICAL CONSIDERATIONS RELATING TO THE TRIAL

The proposed study is an observational study with no alterations to participant's usual routine care. No research-related interventions will be introduced. In all cases, participating centres must submit the study to their local Institutional Review Board for ethical judgment and obtain documentation

to confirm that the trial has been subject to IRB/IEC review and given approval/favourable opinion. Informed consent forms and any other written information to be provided to the parents/guardians, as well as any advertisement for subject recruitment (if used), should also be submitted for IRB/IEC review. Ethics Approval and all other local regulatory requirements must be obtained prior to commencing recruitment.

The consent form will be obtained as follows.

- Elective cases: The parents/guardians will be presented with Patient Information Sheet during the preoperative consultation or on the ward prior to anaesthesia management and individual written consent will be sought if necessary during the consultation or in the holding bay or anaesthetic room immediately prior to anaesthesia.

- Children having urgent or emergency procedures: Study data will be recorded and retrospective consent if necessary will be sought afterwards (and up to 48 hours following admission).

The study co-ordinator provides a template of Patient Information Sheet and Participant's Informed Consent and Authorised Informed Consent in English (see Appendix 1A and 1B).

All translation and Adaptation of the Appendix 1A and 1B should be sent to ESA the Sponsor. Guidance published by the Sponsor should be follow.

IX. DATA HANDLING AND RECORD KEEPING

Participating hospitals will be provided with data acquisition sheets (CRF) that enable standardised recording of all patients' parameters.

Thereafter the data are collected in an anonymous fashion; the data will be coded through a patient identification number (PIN) in the electronic CRF. No patient names, patient initials or hospital patient numbers are collected on the paper CRF or collected electronically. To facilitate patient follow-up the paper CRF is provided with a CRF coversheet: the patient confidential identification CRF Coversheet. This form matches each PIN to the individual patient. After completing the follow-up, this cover page will be detached from the CRF and filed separately in a secure place in each participating centre. The anonymised data acquisition sheet (CRF) will then be used by the local institution to fill in the electronic case report form (eCRF). No names are collected electronically or kept on the data acquisition form. The paper CRFs will be stored behind a lock at the local site. Data will be handled confidentially and centres will keep all data stored for the length of the study and the time foreseen by local rules, but at least for a period of 10 years from the moment of the study completion. Each centre will maintain an Investigator File including: protocol,

IRB judgment, E.C. approval (if applicable), local investigator delegation log, local translation of informed consent form (if applicable), signed informed consent forms (if applicable), etc. All handling of personal data will comply with the GCP Guidelines. All collected data will remain the property of the Sponsor.

X. PUBLICATION POLICY

After submitting grant proposal, recruitment of patients, data acquisition, cleaning and analysis of the data obtained, authorship will be distributed according to differences in investment. Each participating centre including at least 5 patients can designate one collaborator that will be mentioned in the publication. Furthermore, for each additional 10 patients included, one more collaborator can be designated. These collaborators will be mentioned in the manuscript and will be traceable via PubMed. Also, on request, centres will be allowed to use their data. Proposals for secondary analyses can be submitted to the Steering Committee that will need to approve those analyses and that will revise all papers originating from final analysis prior to submission. Furthermore, the Sponsor of the study (ESA CTN) can use anonymised data for internal analyses and educational purposes.

XI. REFERENCES

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XII. LIST OF SUPPLEMENTS/APPENDICES

1. Template for Patient Documentation:

   1A. Study information sheet for the Patient/Parents/Legal guardians

   1B. Informed Consent Form

2. Case Report Form
3. Definitions and list of interventions
4. Pre-study Survey
5. Telephone call instructions for 90-day follow-up
6. End of study Reporting Form
7. Log sheet for patient

XIII. PROTOCOL HISTORY OF CHANGES

Date &Version	Change	Pages	Section	Change Details
28-AUG-2015 Final v1.0	Original	NA	NA	NA

NECTARINE: NEonate – Children sTudy of Anaesthesia pRactice IN Europe

NECTARINE Screening – Inclusion Form

Inclusion criteria
***Corrected age calculation** A. Baby's age at birth since last mother's menses (gestational age) |__|__| weeks B. Baby's age: number of weeks since birth |__|__| weeks **Corrected age = value of A plus value of B =** |__|__| weeks **Is Corrected age ≤ 60 weeks ☐ Yes ☐ No**
If "YES", INCLUDE patient and enter in the study => Paper CRF and electronic CRF should be completed. If "NO", DO NOT INCLUDE patient in the study => Paper CRF and electronic CRF should NOT be completed.

NECTARINE: NEonate – Children sTudy of Anaesthesia pRactice IN Europe

NECTARINE Patient Confidential Identification CRF Coversheet

This coversheet intends to help site staff and local investigator linking local patient data to the study specific study patient code and this sheet is used to facilitate the task to the investigators, and can be filled to your convenience. After completing follow-up, this coversheet should be saved apart from the CRF and filed separately in a secure place. The information on this coversheet will NOT be collected in the CRF. It is for local use ONLY.

IDENTIFYING DATA			
A	**Date paper CRF created**	|__|__| / |__|__|__| / |__|__|__|__| (dd/Mmm/YYYY)	
B	**Date of birth**	|__|__| / |__|__|__| / |__|__|__|__| (dd/Mmm/YYYY)	
C	**Identification** (fill in with available data – only for local follow-up use)**:**	Patient Hospital/local Identification Number (handwritten or sticker): Child's First name: Child's Last name:	
		Family Address:	
		Parent Name: Phone: Email:	Phone number to be used for the 90 days Follow up:
		Family doctor Name: Phone: email:	

Record here multiple anaesthesia dates (if applicable):		1 |__|__|/|__|__|__|/|__|__|__|__|	2 |__|__| / |__|__|__|/|__|__|__|__|
3|__|__|/|__|__|__|/|__|__|__|__|	4|__|__|/|__|__|__|/|__|__|__|__|	5 |__|__|/|__|__|__|/|__|__|__|__|	6 |__|__| / |__|__|__| /|__|__|__|__|
7|__|__|/|__|__|__|/|__|__|__|__|	8|__|__|/|__|__|__|/|__|__|__|__|	9|__|__|/|__|__|__|/|__|__|__|__|	10|__|__| / |__|__|__|/|__|__|__|__|

Completion progress of the study forms:	**Paper CRF**	**OpenClinica electronic CRF**
CRF1: (complete 1x)		

- **Patient Data & Medical History**	☐	☐
CRF2: (repeat for each anaesthesia) - **Anaesthesia Data Intraoperative Data** - **Interventions during anaesthesia** - **Recovery Room**	 ☐ ☐ ☐	 ☐ ☐ ☐
CRF3: (complete 1x after last anaesthesia) - **CRF3-A: Follow Up at 30 days** - **CRF3-B: Follow Up at 90 days**	 ☐ ☐	 ☐ ☐

Appendix 2 - CRF

NECTARINE: NEonate – Children sTudy of Anaesthesia pRactice IN Europe

NECTARINE Case Report Form

CRF 1: Preoperative (Non-Repetitive = 1 per patient)			
PATIENT DATA			
1	**Study Subject ID:**	|__|__|__|-|__|__|__|-|__|__|__| *Enter Study Subject ID in this format xxx-xxx-xxx 3 digit code for the country, 3 digit code for the hospital and 3 digit individual patient number*	
2	**Informed consent applicable?** *(choose no if local authorities/ethics gave written exemption of the consent process)* ☐ No ☐ Yes	2.1 *If yes, was consent obtained?* ☐ No ☐ Yes	
		*2.1.1 If obtained, **enter** date of Informed Consent* ***in this format** dd-Mmm-YYYY (Month in English starting with capital letter)* |__|__|- |__|__|__| -|__|__|__|__|	
3	**Gestational age at birth**	|__|__| weeks [22-40]	
4	**Birth weight:**	|__|.|__|__||__| kg [0.000-9.999]	
5	**Gender:**	☐ Male ☐ Female	
6	**Maternal medications and health issues during pregnancy:**	☐ No ☐ Yes ☐ Info not available	6.1 *If yes (tick all that apply):* ☐ NSAID, Aspirin ☐ Anti-hypertensive drugs ☐ Alcohol/opiates/narcotics ☐ Preeclampsia / Eclampsia ☐ If other, not above reported, tick here
7	**Mode of delivery:**	*tick single most appropriate*: ☐ Vaginal ☐ Caesarean Section ☐ Info not available	
8	**APGAR score:**	1 minute: |__|__| [00-10] ☐ info not Available	
9		5 minutes: |__|__| [00-10] ☐ info not Available	
10	**Has the child any known congenital abnormality?**	☐ No ☐ Yes	10.1 *If yes, tick all that apply (do not ask the parents for this. It should be filled from the medical record):* ☐ Known or suspected myopathy ☐ Congenital heart disease ☐ Known or suspected metabolic disorder ☐ Chromosomopathy ☐ Other (non-cardiac) congenital malformations

CRF2: ANAESTHESIA DATA (Repeat CRF2 for each anaesthesia)

I. MEDICAL HISTORY

1	**History of apnoea or respiratory support?**	☐ No ☐ Yes	1.1 *If yes, specify (tick all that apply):* ☐ Methyl-xanthine (caffeine) ☐ ETT ☐ CPAP ☐ O_2
2	**History of Intra-Ventricular-Haemorrhage:**	☐ No ☐ Yes	2.1 *If yes, provide grade:* |__| [0-4] ☐ Grade not available
3	**History of ECMO support:**	☐ No ☐ Yes	
4	**History of patent ductus arteriosus (PDA):**	☐ No ☐ Yes	4.1 *If yes, was treated? (tick all that apply):* ☐ No treatment ☐ Treated surgically ☐ Treated medically
5	**History of previous surgery?**	☐ **No** ☐ **Yes**	5.1 *If yes, specify number of previous surgeries:* |__|__| [1-10] 5.2 *If yes, is current surgery due to a complication/incomplete/re-do previous surgery:* ☐ No ☐ Yes

II. CURRENT MEDICAL CONDITION (THE DAY OF ANAESTHESIA)

1	**Study Subject ID:** |__|__|__|-|__|__|__|-|__|__|__|	2	**Subject multiple anaesthesia #** *Number of this anaesthesia within NECTARINE:* |__|__| [01-10]
3	**Baby's age on day of anaesthesia:** |__|__| weeks [0-40] & |__| days [0-6]	4	**Weight on day of anaesthesia:** |__|.|__|__|__| kg [0.000-9.999]
5	**Where was the child admitted from?** ☐ Admitted from home ☐ Admitted from ward ☐ Admitted from another hospital ☐ Admitted from ICU	6	**Child breathing condition the day of anaesthesia:** ☐ No oxygen, no ventilation assistance ☐ Patient under spontaneous ventilation with O_2 ☐ Patient under NIV with CPAP ☐ Patient INTUBATED on conventional ventilation ☐ Patient INTUBATED on HFOV ☐ Patient on ECMO 6.1 *If patient already intubated, what is the main reason for ETT:* ☐ Clinically unstable ☐ For surgery ☐ Other
7	**Place where procedure is performed:** *(choose single)* ☐ Operating Room/diagnostic suite ☐ ICU	8	**Is the child on one or more than the follow medications?** *(tick all that apply)* ☐ Benzodiazepines ☐ Opioids ☐ Dexmedetomidine/Clonidine ☐ Muscle relaxant ☐ Ketamine ☐ Vasopressors/Inotropes (e.g.noradrenaline, dopamine, etc.) ☐ Diuretics ☐ Other than the above reported medications

III. ASSESSMENT OF THE CHILD AT THE TIME OF ANAESTHESIA

1	**Current RESPIRATORY and airway problems:** ☐ No ☐ Yes ☐ info not available 1.1 *If yes, (tick all that apply):* ☐ Broncho-pulmonary dysplasia ☐ Laryngo-tracheomalacia ☐ Stridor ☐ Pneumonia ☐ Other 1.1.1 *If other, specify:*	**2**	**Current CARDIOVASCULAR problems:** ☐ No ☐ Yes ☐ info not available 2.1 *If yes, (tick all that apply):* ☐ Cardiac murmur of any kind ☐ Patent Ductus Arteriosus ☐ Pulmonary Hypertension (ultrasound or catheter diagnosis) ☐ Cyanosis (Right to Left shunt) ☐ Other 2.1.1 *If other, specify:*
3	**Current METABOLIC problems:** ☐ No ☐ Yes ☐ info not available 3.1 *If yes, (tick all that apply):* ☐ Sepsis ☐ Jaundice (Increased Bilirubin) ☐ Metabolic alkalosis ☐ Metabolic acidosis ☐ Other 3.1.1 *If other, specify:*	**4**	**Current neurologic/BRAIN problems:** ☐ No ☐ Yes ☐ info not available 4.1 *If yes, (tick all that apply):* ☐ Hydrocephalus (with or without ventricular shunt) ☐ Seizures ☐ Periventricular leucomalacia ☐ Retinopathy of prematurity ☐ Other 4.1.1 *If other, specify:*
5	**Current RENAL problems:** ☐ No ☐ Yes ☐ info not available 5.1 *If yes, (tick all that apply):* ☐ Renal insufficiency ☐ Renal dysplasia ☐ Other *5.1.1 If other, specify:*	**6**	**ASA score** *(tick single most appropriate)* ☐ I *(only applicable if > 3 months)* ☐ II ☐ III ☐ IV ☐ V

IV. BASELINE PHYSIOLOGICAL & METABOLIC PARAMETERS

Physiological parameters*: fill all available items based on what you consider as baseline physiological parameters*

1	**Specify when baseline parameters were taken?** *(tick single most appropriate)*	☐ Medical record (within the 24 hrs) ☐ Before Induction ☐ After induction, first measurement	
1.1	**Systolic blood pressure**	|__|__|__| mmHg [0-199]	☐ Not Available
1.2	**Mean blood pressure**	|__|__|__| mmHg [0-199]	☐ Not Available
1.3	**Diastolic blood pressure**	|__|__|__| mmHg [0-199]	☐ Not Available
1.4	**Heart Rate**	|__|__|__| beats/min. [0-299]	☐ Not Available
1.5	**NIRS**	|__|__|__| [0-100]	☐ Not Available
1.6	**Pre-ductal SpO_2**	|__|__|__| % [0-100]	☐ Not Relevant (only in the neonate) ☐ Not Available
1.7	**Post-ductal SpO_2**	|__|__|__| % [0-100]	☐ Not Relevant (only in the neonate) ☐ Not Available
1.8	**Arterial/Venous CO_2**	|__|__| mmHg [20-99] ☐ Arterial ☐ Venous	☐ Not Available
1.9	**Body temperature**	|__|__|.|__| °C [34.0-40.0]	☐ Not Available

Metabolic parameters:
fill available items for metabolic parameters, referring to preoperative assessment or early intraoperative

2	**Na** |__|__|__|.|__|	*Select unit used* ☐ mEq/L [99.9-199.9] ☐ mMol/L [99.9-199.9]	☐ Not Available
3	**Hb** |__|__|.|__|	*Select unit used*	☐ Not Available

		☐ g/dL [0.0-20.0] ☐ mMol/L [0.0-20.0]
4	**Glucose** |__|__|__|	*Select unit used* ☐ Not Available ☐ mg/dL [0.0-999] ☐ mMol/L [0.0-50]

V. INDICATION

1 **2**	**Date and time of anaesthesia (induction):**	|__|__|- |__|__|__| - |__|__|__|__| dd/Mmm/yyyy [>=01-Mar-2016] |__|__|:|__|__| HH:MM [0-23]: [0-59]
3 **4**	**Date and time surgery/procedure start:**	|__|__|- |__|__|__| - |__|__|__|__| dd/Mmm/yyyy [>=01-Mar-2016] |__|__|:|__|__| HH:MM [0-23]: [0-59]
5	**Degree of urgency:**	*(choose single most appropriate)* ☐ Elective ☐ Semi-elective/Urgent ☐ Emergency
6	**Type of procedure:**	☐ Surgical => complete sections 6.1 to 6.10 ☐ Non-Surgical procedure=> complete section 6.11

If SURGICAL painful procedure *(tick single most relevant; tick main surgery if mixed)*:

6.1	**If surgical, indicate: Minimally invasive surgery? (laparoscopy, thoracoscopy,…)** ☐ No ☐ Yes	6.1.1 If yes, was it concluded also as minimal? ☐ No, converted to open surgery ☐ Yes

6.2 Oesophageal, gastro-intestinal surgery:

☐ No ☐ Yes

6.2.1 *If yes, specify*: *(tick most relevant; tick main surgery if mixed)*

☐ Anorectal malformations (PSARP, …)

☐ Biliary atresia: Kasai procedure

☐ Choledochal cyst excision

☐ Diaphragmatic hernia

☐ Fundoplication

☐ Gastrostomy tube

☐ Inguinal Hernia Repair (unilateral or bilateral)

☐ Intestinal obstruction

☐ Liver biopsy

☐ Necrotising Enterocolitis

☐ Oesophageal atresia with or without tracheo-oesophageal fistula

☐ Omphalocoele, gastroschisis

☐ Pyloric stenosis

☐ Ileostomy/Colostomy

☐ Other 6.2.1.1 *If other, specify:*

6.3 Thoracic surgery:	**6.4 Cardiac surgery:**
☐ No ☐ Yes	☐ No ☐ Yes
6.3.1 *If yes, specify: (tick single most relevant)*	6.4.1 *If yes, specify: (tick single most relevant)*
☐ Congenital lung lesions (Cystic adenomatous malformation)	☐ Aortopexy
☐ Lung biopsy	☐ Arterial switch operation or other treatment for transposition of great vessels
☐ Mediastinal mass	☐ Blalock shunt
☐ Lobectomy	☐ Closure of PDA
☐ Other 6.3.1.1 If other, specify:	☐ Coarctation
	☐ Norwood procedure
	☐ Pulmonary artery banding
	☐ Tetralogy of Fallot
	☐ Total abnormal venous return
	☐ Other 6.4.1.1 *If other, specify:*
6.5 Genitourinary surgery:	**6.6 Neurosurgery:**
☐ No ☐ Yes	☐ No ☐ Yes
6.5.1 *If yes, specify: (tick single most relevant)*	6.6.1 *If yes, specify: (tick single most relevant)*
☐ Peritoneal dialysis catheter	☐ Closure of myelomeningocoele
☐ Correction of ureteropelvic junction	☐ Exploration and decompression spinal canal
☐ Cystostomy	☐ Synostosis
☐ Nephrectomy	☐ Ventricular shunt to abdominal cavity
☐ Nephroureterectomy, Pyeloplasty	☐ Ventriculostomy

☐ Orchidopexy, Torsion of testis ☐ Ovarian cyst ☐ Circumcision for medical reason ☐ Ritual circumcision ☐ Urethral valves ☐ Other 6.5.1.1 *If other, specify:*	☐ Other 6.6.1.1 *If other, specify:*
6.7 Ophthalmology surgery: ☐ No ☐ Yes 6.7.1 *If yes, specify: (tick single most relevant)* ☐ Cryotherapy destruction of chorioretinal lesion ☐ Laser destruction of chorioretinal lesion ☐ Phacofragmentation & aspiration of cataract ☐ Probing of nasolacrimal duct ☐ Other 6.7.1.1 If other, specify:	**6.8 ENT-Plastic surgery:** ☐ No ☐ Yes 6.8.1 *If yes, specify: (tick single most relevant)* ☐ Choanal atresia ☐ Cleft lip ☐ Excision of lesion of external ear ☐ Laser treatment of laryngeal lesions ☐ Lingual frenotomy ☐ Repair and plastic operations on trachea ☐ Other 6.8.1.1 *If other, specify:*
6.9 Orthopaedic surgery: ☐ No ☐ Yes 6.9.1 *If yes, specify: (tick single most relevant)* ☐ Arthrotomy ☐ Clubfoot repair ☐ Excision of soft tissue lesion ☐ Internal fixation of bone ☐ Supernumerary digit (polydactyly) ☐ Other 6.9.1.1 *If other, specify:*	**6.10 Dermatology surgery:** ☐ No ☐ Yes 6.10.1 *If yes, specify: (tick single most relevant)* ☐ Biopsy of skin and subcutaneous tissue ☐ Excision of skin and subcutaneous tissue ☐ Incision with drainage of skin and subcutaneous tissue (i.e.: anal abscess, etc.) ☐ Operation on skin and subcutaneous tissue ☐ Other 6.10.1.1 *If other, specify:*

If NON-SURGICAL procedure *(tick single most relevant; tick main non-surgery if mixed)*:

6.11	☐ Angiography/embolization	☐ Gastroenterology
	☐ Biopsy	☐ Infiltration or punction
	☐ Bronchoscopy	☐ MRI (Magnetic rad. Imaging)
	☐ Burns dressing	☐ Ophthalmologic examination/Laser
	☐ Cardiac lab (Percutaneous valvuloplasty)	☐ Pericardial or pleural drainage

	☐ CT-Scan ☐ Cystoscopy	☐ PICC line/Central venous/Broviac ☐ Other non-surgical 6.11.1 *If other, specify:*
7	**Team involved for the anaesthesia management:** *(specify the number of staff members in charge of the patient)*	|__| [0-5] Senior anaesthesiologist (> 5 years from certification) |__| [0-5] Junior anaesthesiologist (< 5 years from certification) |__| [0-5] Anaesthesiologist in training |__| [0-5] Anaesthetic nurse/technician |__| [0-5] ICU personnel (neonatologist or paediatrician)
8	**Monitoring:** *(tick all that apply)*	☐ Standard (ECG, SpO_2 , anaesthetic agent, capnography, NIBP, temp) ☐ Arterial ☐ Central venous line ☐ NIRS
9	**Anaesthesia Technique:** *(tick single most appropriate)*	☐ General anaesthesia (fill in section V-1) ☐ Regional anaesthesia alone (fill in section V-2) ☐ Combined general and regional anaesthesia (fill in section V-1 & V-2)

Section V-1. GENERAL ANAESTHESIA

1	**Anaesthesia induction**	*(tick the way of administration of first drug that was administered)* ☐ **Inhalational** ☐ **Intravenous** ☐ **Intramuscular**

Please specify Induction Drug: *(tick all drugs used)*

1.1	☐ Sevoflurane	**1.6**	☐ Propofol	**1.11** ☐ Opioid	
1.2	☐ Halothane	**1.7**	☐ Thiopentone	*If opiate(s), specify:*	
1.3	☐ Desflurane	**1.8**	☐ Ketamine	1.11.1 ☐ Sufentanil	1.11.4 ☐ Remifentanil
1.4	☐ Isoflurane	**1.9**	☐ Atropine	1.11.2 ☐ Fentanyl	1.11.5 ☐ Morphine
1.5	☐ Midazolam	**1.10**	☐ Etomidate	1.11.3 ☐ Alfentanil	1.11.6 ☐ Other

2	**Neuromuscular blocking agent (NBA) used?** ☐ No ☐ Yes	*2.1 If yes, specify which NBA:* ☐ Succinylcholine ☐ Cisatracurium ☐ Atracurium ☐ Rocuronium ☐ Vecuronium
		2.2 If yes, was NBA given prior or after intubation?

		☐ Prior ☐ After			
		2.3 If yes, reversal at the end? ☐ Neostigmine ☐ Sugammadex ☐ No			
3	**Maintenance drugs given?** ☐ No ☐ Yes, specify all drugs for maintenance *(tick all drugs used)*:				
3.1	☐ Sevoflurane	**3.6**	☐ Propofol	**3.11** ☐ Opioid	
3.2	☐ Halothane	**3.7**	☐ Thiopentone	*If opiate(s), specify:* 3.11.1 ☐ Sufentanil	3.11.4 ☐ Remifentanil
3.3	☐ Desflurane	**3.8**	☐ Ketamine	3.11.2 ☐ Fentanyl	3.11.5 ☐ Morphine
3.4	☐ Isoflurane	**3.9**	☐ Atropine	3.11.3 ☐ Alfentanil	3.11.6 ☐ Other
3.5	☐ Midazolam	**3.10**	☐ Etomidate		
4	**Carrier gas:** *(choose single)* ☐ Oxygen ☐ Oxygen + N_2O ☐ Oxygen + air ☐ Air ☐ Other				
5	**Is vasopressor or inotropic** *(i.e. dopamine, norepinephrine, etc.)* **drug infusion part of the anaesthesia management from the beginning?**				☐ No ☐ Yes

Section V-2. REGIONAL ANAESTHESIA

1	**Specify block** *(choose single most appropriate)*:		**2**	**Regional catheter for continuous analgesia?**
☐ Spinal	☐ TAP			
☐ Caudal	☐ Intercostal		☐ No ☐ Yes	
☐ Lumbar epidural	☐ Paraumbilical			
☐ Thoracic epidural	☐ Penile			
☐ Upper limb	☐ Craniofacial			
☐ Lower limb	☐ Infiltration of the wound			
☐ Ilio-inguinal	☐ Other, not above specified			

VI. AIRWAY MANAGEMENT

1	**Specify type of interface for airway management** *(tick single most appropriate):*		
☐ **Face Mask**	☐ **SGAW (Supraglottic Airway)**	☐ **Tracheostomy**	
☐ **ETT (Endotracheal tube)**	☐ **Nasal Probe/CPAP/Non-Invasive ventilation**	☐ **None**	

If ETT			
=>	**1.1**	Indicate Tube Type: ☐ Cuffed ☐ Uncuffed	
=>	**1.2**	Intubation route: ☐ Oral ☐ Nasal	
=>	**1.3**	Cormack-Lehane score: *(tick single most appropriate)* ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ Unknown/already intubated	

VII. VENTILATION

1	**Ventilation type:**	1.1 *If controlled ventilation specify: (tick single most appropriate)*

	(choose single most appropriate) ☐ **Spontaneous ventilation** ☐ **Assisted ventilation** ☐ **Controlled ventilation**	☐ Volume controlled (VC) ☐ Pressure controlled (PC) ☐ Pressure regulated volume controlled (PRVC) ☐ High Frequency Oxillatory Ventilation (HFOV)	
		1.1.1 *For VC, PC, PRVC, please specify if initial setting is available?* ☐ No ☐ Yes	*If yes, specify* 1.1.1.1 *PIP* |__|__| cm/H_2O [0-99] 1.1.1.2 *PEEP* |__|__| cm/H_2O [0-20] 1.1.1.3.FiO_2 |__|.|__|__| [0.21-1.0]

VIII. END OF ANAESTHESIA/PROCEDURE TIMING

1	**Date end of surgery/procedure/anaesthesia:**	|__|__|- |__|__|__| -|__|__|__|__| [>=01-Mar-2016]
2	**Time End of surgery/procedure:**	|__|__|:|__|__| HH:MM [0-23]:[0-59]
3	**Time End of anaesthesia:**	|__|__|:|__|__| HH:MM [0-23]:[0-59]

IX. PERIOPERATIVE INTERVENTIONS

For definitions of Interventions for critical events please refer to last page of CRF

1	**Have you performed a medical intervention/treatment IN RESPONSE to a critical event?**	☐ No, go to Follow-up data ☐ Yes, complete the perioperative interventions section

If yes, fill in all the appropriate sections:	Section V CARDIOVASCULAR CONDITION
Section I AIRWAY MANAGEMENT	Section VI BODY TEMPERATURE
Section II OXYGENATION	Section VII BRAIN OXYGENATION
Section III ALVEOLAR VENTILATION	Section VIII ANAEMIA
Section IV METABOLIC	

I INTERVENTION FOR DIFFICULT AIRWAY MANAGEMENT *defined as more than 2 unsuccessful attempts of intubation by direct laryngoscopy, which require alternative strategies for achieving successful intubation.*

1	**Has difficult AIRWAY MANAGEMENT, which needed intervention(s), occurred?**	☐ No ☐ Yes (fill in all sub-items)

1.1 Specify Intervention(s) for difficult intubation: *(tick all that apply)* ☐ Change of laryngoscope blades ☐ Supra-glottic airway device ☐ Use of video-assisted intubation ☐ Use of air-track ☐ Use of stylet or bougie ☐ Use of fiberoptic bronchoscopy ☐ Help from ENT colleague or 2nd senior anaesthesiologist ☐ Emergency tracheostomy ☐ Blind intubation ☐ Other	1.1.1 *If other, specify:*

1.2 Was the difficult intubation an unplanned occurrence?	☐ No ☐ Yes
1.3 Was it associated with difficult face-mask ventilation?	☐ No ☐ Yes
1.4 Was a significant drop in oxygenation associated?	☐ No ☐ Yes
1.5 Was significant bradycardia associated?	☐ No ☐ Yes
1.6 Number of attempts until successful intubation:	|__|__| [3-20]

1.7 Outcome of event: *(tick single most appropriate)*	☐ Successful intubation ☐ Unsuccessful intubation, procedure performed under face or laryngeal mask ☐ Unable to intubate, patient woken up from anaesthesia

II OXYGENATION: Intervention for hypoxaemia *defined as an action or a pharmacological treatment aimed at improving poor oxygenation and triggered by low SpO_2 and/or PaO_2.*		
2	**Has POOR OXYGENATION, which needed intervention(s), occurred?**	☐ No ☐ Yes (fill in all sub-items)
2.1	**Specify Intervention(s) for improving oxygenation:** *(tick all that apply)* ☐ Emergency/unplanned intubation (if patient previously not intubated) ☐ Change/repositioning of an accidentally dislocated or obstructed tracheal tube ☐ Need for FiO_2 higher than for routine practice (or persistent need of FiO_2 = 1) ☐ Need for PEEP higher than for routine practice ☐ Need for prolonged manual ventilation in already intubated/ventilated patient ☐ Recruiting manoeuvre(s) ☐ Switch from conventional to non-conventional ventilation (HFOV) ☐ Drainage of an acute pneumothorax ☐ Pharmacological treatment of laryngospasm ☐ Pharmacological treatment of bronchospasm ☐ Other	2.1.1 *If other, specify:*
2.2	**Time of occurrence of hypoxaemia** *(only if more than one, tick all that apply)* ☐ Induction ☐ Maintenance ☐ Awakening ☐ PACU	
2.3	**Number of poor oxygenation events that required intervention(s) during anaesthesia** *(tick single most appropriate)* ☐ Once ☐ Twice ☐ Three times or more, or persistent poor oxygenation	
2.4	**SpO_2 threshold that triggered intervention** *(choose single -refer to the most severe, if more than one):* ☐ < 90% ☐ < 85% ☐ < 80%	

2.5	**PaO_2 value that triggered intervention:** |__|__|__| *Specify units used:* ☐ Not Available ☐ *kPa* [0-100] ☐ *mmHg* [0-999]	
2.6	**provide approximate duration of hypoxaemia**: |__|__|__| min. [1-999] ☐ Not Available	
2.7	**Outcome of event?** *(tick single most appropriate)*	☐ Successful - oxygenation improved ☐ Persistent Hypoxaemia ☐ Deterioration of oxygenation despite specific intervention(s)
2.8	**Was the poor oxygenation accompanied by a significant change in rSO_2 by NIRS?**	☐ No ☐ Yes. *If yes, fill in section VII (Brain oxygenation).* ☐ NIRS not available
2.9	**Was hypoxaemia associated with hypoventilation (hypercapnia)**	☐ Yes. *If yes, fill in section III (Intervention for HYPO or HYPERcapnia)*

		☐ No
III Intervention for HYPO or HYPERcapnia (without associated hypoxaemia) *defined as an action to correct an alteration in End-tidal carbon dioxide ($ETCO_2$) and/or arterial/venous blood CO_2* level		
3	**Has altered CO_2, which needed intervention(s), occurred?**	☐ No ☐ Yes (fill in all sub-items)
3.1	**Specify Intervention(s) for improving alveolar ventilation** ☐ Change of ventilation modality ☐ Change of airway device (from face mask/SGAW to ETT) ☐ Change of the dead-space ☐ Need for Peak Inspiratory Pressure higher than for routine practice ☐ Prolonged/persistent manual ventilation ☐ Alveolar recruitment manoeuvre(s) ☐ Other	3.1.1 *If other, specify:*
3.2	**Number of interventions during anaesthesia:** ☐ Once ☐ Twice ☐ Three times and more, or persistent inadequate alveolar ventilation	
3.3	**$ETCO_2$ threshold that triggered intervention (refers to the most severe, if more than one):** *Specify units used:* |__|__|__| ☐ *kPa* [0-100] ☐ *mmHg* [0-999]	
3.4	**, $PaCO_2$ value that triggered intervention:** *Specify units used:* |__|__|__| ☐ *kPa* [0-100] ☐ *mmHg* [0-999] ☐ Not available	
3.5	**Outcome of event?** *(tick single most appropriate)* ☐ Successful/ improvement ☐ Persistent difficult ventilation	**3.6 Were the CO_2 changes accompanied by a change in rSO2 by NIRS?** ☐ No ☐ Yes. *If yes, fill in section VII (Brain oxygenation).* ☐ NIRS not available
IV METABOLIC Intervention *defined as an action for correcting high/low blood glucose and/or Na^+:*		
4	**Have you performed treatment(s) for high/low glucose and/or Na^+?**	☐ No ☐ Yes (fill in all sub-items)

4.1	**Specify Intervention(s) for high/low glucose:** *(tick all that apply)*	☐ Administration of glucose (iv or continuous infusion) ☐ Stop i.v. glucose or fluids containing glucose ☐ Onset of insulin treatment
4.2	**Specify Intervention(s) for high/low Na^+:** *(tick all that apply)*	☐ Administration of additional Na+ (fluids or electrolytes) ☐ Stop i.v. glucose or hypotonic solutions
4.3	**What was the <u>glucose</u> and/or <u>Na^+</u> value(s) that triggered intervention(s):**	*Select units used:* ☐ Glucose |__|__|__| ☐ mMol/L [0-50] ☐ mg/dL [0-999] ☐ Na^+ |__|__|__|. |__| ☐ mMol/L [99-199] ☐ mEq/L [99.9-199.9]
4.4	**Outcome of event?** *(tick single most appropriate)*	☐ Successful - parameter corrected ☐ Persistent disorder

V Intervention for CARDIOVASCULAR INSTABILITY
defined as an intervention or a medical treatment to control cardio-vascular instability. This clinical condition can be triggered by the occurrence of hypo- or hyper-tension and/or cardiac rhythm disturbances on the ECG.

5	**Has CARDIOVASCULAR INSTABILITY, which needed intervention(s), occurred?**	☐ No ☐ Yes (fill in all sub-items)
5.1	**Was the intervention/treatment based on blood pressure:** ☐ No ☐ Yes	
5.2	**Number of interventions during anaesthesia:** ☐ Once ☐ Twice ☐ Three times and more	
5.3	**Specify Intervention(s) based on Blood Pressure and/or Cardiac Output: *Tick all that apply.*** ☐ Bolus of > 20 ml/kg of crystalloids (also 2 x 10 ml/kg) ☐ Bolus of > 10 ml/kg of albumin ☐ Bolus of > 10 ml/kg of other colloids ☐ Administration of Fresh Frozen Plasma for hypovolemia leading to C-V instability ☐ Administration of Packed Red Cells for C-V instability ☐ Other 5.3.1 *If other, specify:*	
5.4	**Blood pressure value that triggered intervention:** *Choose the one that have triggered your intervention:* ☐ *Systolic* ☐ *Mean*	5.4.1 *Indicate value:* |__|__|__| mmHg [0-999]

	☐ *Diastolic*	
5.5	**Total volume given as boluses with the aim to normalise blood pressure (do not include volume of fluids for maintenance):**	*Indicate value:* |__|__|__| ml/kg [10-999]
5.6	**Time of occurrence** *(tick all that apply, only if more than one episode):*	☐ Induction ☐ Maintenance ☐ Whilst in PACU
5.7	**Was one or more of the following drugs given for BLOOD PRESSURE or CARDIAC OUTPUT instability (report only if drug(s) are given in response to a critical event; do not report if drugs are given as part of "usual protocol"):**	

5.7.1 ☐ Ephedrine	5.7.6 ☐ Dobutamine
5.7.2 ☐ Phenylephrine	5.7.7 ☐ Epinephrine/Adrenaline
5.7.3 ☐ Noradrenaline/Norepinephrine	5.7.8 ☐ Milrinone
5.7.4 ☐ Dopamine	5.7.9 ☐ Levosimendan
5.7.5 ☐ Nitroglycerine	5.7.10 ☐ Nitroprusside

5.8	**Blood pressure value that triggered DRUG administration:** *Choose the one that have triggered the intervention:* ☐ *Systolic* ☐ *Mean* ☐ *Diastolic*	*5.8.1 Indicate value:* |__|__|__| mmHg [0-999]
5.9	**Time of occurrence** *(tick all that apply, only if more than one episode):*	☐ Induction ☐ Maintenance ☐ Whilst in PACU
5.10	**Was the intervention/treatment based on ECG disturbance:**	☐ No ☐ Yes
5.11	**If YES, specify Intervention(s) triggered by heart rate/ECG disturbances:**	☐ Atropine i.v. (ONLY for treatment, not for prevention) ☐ Glycopyrolate i.v. (ONLY for treatment, not for prevention) ☐ Epinephrine ☐ Ca++ ☐ Mg++ ☐ Lidocaine i.v. ☐ Amiodarone i.v. ☐ Electric defibrillation ☐ External pacing ☐ Chest compression < 1 min. ☐ Cardiopulmonary resuscitation (CPR) ☐ Other 5.11.1 *If other, specify:*
5.12	**If intervention was based on heart rate or ECG disturbance, please specify threshold value that triggered intervention (zero if cardiac arrest):**	|__|__|__| beats/min. [0-300]
5.13	**Approximate duration of instability:**	|__|__|__| min. [1-999]
5.14	**Time of occurrence** *(tick all that apply, only if more than one episodes):*	☐ Induction ☐ Maintenance ☐ Whilst in PACU
5.15	**Outcome of event:**	☐ Successful treatment ☐ Persistent cardiovascular instability
5.16	**Was the haemodynamic instability accompanied by a change in rSO_2 by NIRS?**	☐ No ☐ Yes. *If yes, fill in section VII (Brain oxygenation.* ☐ NIRS not available
VI Intervention for high/low BODY TEMPERATURE		

defined as an intervention for core body temperature derangement, in either direction (hypo/hyper).			
6	**Has BODY TEMPERATURE ALTERATION which needed intervention(s), occurred?**	☐ No ☐ Yes (fill all sub-items)	
6.1	**Specify interventions triggered by body temperature:**	☐ New onset of warming fluids *(if not already in use)* ☐ Active warming with blanket *(if not already in use)* ☐ Cooling fluids ☐ Active cooling body ☐ Other 6.1.1 *If other, specify:*	
6.2	**If yes, specify the threshold trigger:** *(tick single most appropriate)*	6.2.1 Location of probe: ☐ Oesophageal ☐ Rectal ☐ Cutaneous	6.2.2 Value of trigger: |__|__| °C [30-45]
6.3	**Outcome of event:** *(tick all that apply)*	☐ Uneventful - successful treatment ☐ Cardiovascular instability ☐ Coagulopathy	

VII BRAIN OXYGENATION Intervention *Defined as: when brain oxygenation with NIRS monitoring is part of clinical care, the occurrence of low rSO_2 and/or a drop in rSO_2. Any action or medical treatment to increase brain oxygenation will be also reported.*		
7	**Has any low rSO_2 and/or drop in regional cerebral oxygenation (rSO_2) occurred?**	☐ No ☐ Yes ☐ NIRS was not available
7.1	**Specify Interventions triggered by NIRS monitoring:**	☐ None ☐ Alteration in ventilation ☐ Intervention for systemic blood pressure ☐ Intervention for oxygenation ☐ Intervention for haemoglobin ☐ Intervention for cardiac output (Inotropes or via CPB in cardiac surgery) ☐ Other 7.1.1 *If other, specify:*
7.2	**If intervention, was this based on % drop or absolute value?** ☐ Absolute value (fill in 7.3) ☐ Percentage drop (fill in 7.4)	

7.3	**If absolute value specify rSO_2 value:** **|__|__|__| %** [0-100]	**7.4 If percentage specify the percentage drop from baseline:** **|__|__|__|%** [20-100]
VIII	**Packed Red Cells administered?** (if PRC given for cardiovascular instability, please refers to section V)	
8	**Were Packed Red Cells administered for ANAEMIA as primary reason?** ☐ No ☐ Yes	8.1 *If yes, specify* haemoglobin level that triggered transfusion, |__|__|.|__| *Specify units used:* ☐ g/dL [0.0-20.0] ☐ mMol/L [0.0-20.0] 8.2 Total volume administered intraoperatively : |__|__|__| ml

X. END OF ANAESTHESIA AND UP TO 120 MINUTES (or until PACU discharge)

1	**Where was the child transferred after PACU discharge?** ☐ PICU/NICU ☐ Intermediate Care/High Dependency Unit ☐ Ward ☐ Other
1.1	**If PICU/NICU, was admission UNPLANNED?** ☐ No ☐ Yes
1.1.1	**If YES (unplanned), is PICU/NICU admission due to above reported critical event(s):** ☐ No ☐ Yes
1.2	**Was the child left intubated at PICU/NICU admission?** ☐ No ☐ Yes (fill in item 2)
1.2.1	**If left INTUBATED, was delayed extubation UNPLANNED and/or related to the above reported critical event(s)?** ☐ No ☐ Yes
2	**Relevant postoperative bleeding which needed surgical revision prior to PACU discharge?** ☐ No ☐ Yes
3	**Need for postoperative ECMO?** ☐ No ☐ Yes
4	**Need to leave chest open (only for cardiac surgery)?**

	☐ No ☐ Yes	
5	**In-hospital overnight admission while scheduled as outpatient?** ☐ No ☐ Yes	**5.1 If YES, was delay in hospital discharge due to above reported critical event(s)?** ☐ No ☐ Yes

CRF 3-A: FOLLOW UP AT DAY 30 (Not repeated = 1 per patient)		
Complete 30 days after the LAST anaesthesia (if multiple occurrence) with data from the medical record. *This is mandatory for all patients*		
1	**Was follow-up made after 30 days (+/- 2 days), using the original medical record?** ☐ No ☐ Yes If no, END OF QUESTIONNAIRE	1.1 If yes, date of Day 30 follow-up |__|__| - |__|__|__| - |__|__|__|__| [>=01-Mar-2016]
2	**Patient Status at Day 30** *(tick single most appropriate)*	☐ Discharged to home ☐ Discharged to another hospital ☐ Still in hospital ☐ Still in ICU ☐ Death
2.1	**Date of discharge or death:** |__|__| - |__|__|__| -|__|__|__|__| dd/Mmm/yyyy [>=01-Mar-2016]	**2.2 If death, suspected cause:**
3	**Total day(s) in PICU/NICU (zero never in ICU):** |__|__| days [0-30]	
4	**Total day(s) on ventilation (zero never ventilated):** |__|__| days [0-30]	
5	**Was the patient admitted/re-admitted to PICU/NICU during the 30 days of follow-up (as a separate event from the immediate postoperative period)?** ☐ No ☐ Yes	
6	**MORBIDITY at Day 30 (or day of discharge):** Has the child experienced any complication(s) in the 30 days following anaesthesia?	*Please fill yes or no ONLY if you have access to the medical file / if no access, please tick unknown* ☐ No ☐ Yes (If yes, choose the appropriate complication(s) from 6.1 to 6.6) ☐ Unknown
6.1	**BRAIN/CNS complication?** ☐ No ☐ Yes ☐ info not Available	6.1.1 *If yes, tick all that apply:* ☐ Hypertonia (new onset) ☐ Hypotonia (new onset) ☐ Intracranial bleeding (ultrasound, CT, or MRI) ☐ Intracranial ischaemia (ultrasound, CT, or MRI) ☐ Occurrence of seizures (clinically or EEG)
6.2	**SURGICAL complication?** ☐ No ☐ Yes ☐ info not Available	6.2.1 *If yes, tick all that apply:* ☐ Re-operation for unsuccessful or complicated first surgery ☐ Severe surgical site infection with new onset of antibiotics

		☐ Need for prolonged parenteral nutrition do to surgical complication
6.3	**RESPIRATORY complication?** ☐ No ☐ Yes ☐ info not Available	6.3.1 *If yes, tick all that apply:* ☐ ECMO (Extra Corporeal Membrane Oxygenation) ☐ Failure of weaning with prolonged ventilator support ☐ Need for re-intubation after being extubated ☐ Pleural effusion ☐ Pneumonia ☐ Pneumothorax
6.4	**CARDIO-VASCULAR complication?** ☐ No ☐ Yes ☐ info not Available	6.4.1 *If yes, tick all that apply:* ☐ Arrhythmia ☐ Episode(s) of Cardiac Arrest ☐ Cardiac Ischaemia (elevated troponine) ☐ ECMO (Extra Corporeal Membrane Oxygenation) ☐ Arterial/Venous Embolism ☐ Inotropes-Vasopressors needed (after 1st day) ☐ Venous Thrombosis (on central venous line)
6.5	**LIVER FAILURE?** ☐ No ☐ Yes ☐ info not Available	6.5.1 *If yes, tick all that apply:* ☐ Coagulation Disorders (Increase in INR >2) ☐ Increase in serum bilirubin >300 micromol/L (>10 mg/dL)
6.6	**RENAL INSUFFICIENCY?** ☐ No ☐ Yes ☐ info not Available	6.6.1 *If yes, tick all that apply:* ☐ Continuous renal replacement therapy (CRRT) ☐ Increase creatinine levels necessitating adaptation of medications ☐ Peritoneal dialysis
CRF 3-B: FOLLOW UP AT DAY 90 **(Non-Repetitive = 1 per patient)**		
If patient still at hospital complete with MEDICAL RECORD; if patient is discharged before day 90 to be done with telephone CALL or FACE TO FACE visit)		
1	**Was a follow-up made after 90 days (+/- 2 days) (telephone call or face to face)?** ☐ No ☐ Yes	If no, END OF QUESTIONNAIRE 1.1 *If yes, date of Day 90 follow-up* |__|__| - |__|__|__| - |__|__|__|__| [>=01-Mar-2016]
2	**State at 90 days?**	*Please tick 1 of the following:* ☐ Alive – discharged home between 30 and 90 days (fill in 2.1) ☐ Alive - still in Hospital at 90 days

		☐ Death - between 30 and 90 days (fill in 2.2)
2.1	**Date of discharged (between 30 and 90 days):**	|__|__| - |__|__|__| - |__|__|__|__| [>=01-Mar-2016]
2.2	**Day of death (between 30 and 90 days):**	|__|__| - |__|__|__| - |__|__|__|__| [>=01-Mar-2016]
2.3	**Any hospital re-admission until the 90-day follow-up?** ☐ No ☐ Yes	*2.3.1 If YES, specify* reason for hospital readmission*:*
2.4	**If deceased at 90 days, suspected cause of death:**	*Briefly describe cause of death:*

Appendix 3 – Definitions and list of interventions:

Intervention is an action/medical treatment which is performed **in response to a critical event and/or a physiological parameter derangement** as judged by the anaesthesia team.

The medical treatment given for preventing a critical event will not be considered as an intervention.

1. Interventions for Difficult airway management:	Defined as more than 2 unsuccessful attempts of intubation by direct laryngoscopy, which require alternative strategies.
2. Interventions for Oxygenation:	Defined as an action or a pharmacological treatment performed by the anaesthesia team aimed at improving a status of poor oxygenation. The specific intervention can be triggered by SpO_2 and/or PaO_2.
3. Intervention for Alveolar ventilation:	Defined as an action or a treatment performed by the anaesthesia team aimed at correcting an alteration in CO_2 levels (End-tidal-CO_2 and/or P-arterial/venous CO_2).
4. Interventions for correcting Glycaemia, Na^+ levels:	Defined as a treatment performed by the anaesthesia team aimed at correcting abnormal levels of blood glucose and/or Na, in either direction (hypo/hyper).
5. Intervention for Cardiovascular instability:	Defined as an intervention or a medical treatment to control cardio-vascular instability. This clinical condition can be triggered by the occurrence of hypo- hypertension and/or cardiac rhythm disturbances on the ECG.
6. Intervention for correcting body temperature:	Defined as an intervention for core body temperature derangement, in either direction (hypo/hyper).
7. Interventions induced by poor Brain oxygenation:	Defined as the occurrence of low rSO_2 and/or a drop in rSO_2 when brain oxygenation with NIRS monitoring is part of clinical care. Any action or medical treatment to increase brain oxygenation will also be reported.
8. Packed Red Cells transfusion for Anaemia:	This section will be filled in in case of Packed Red Cell transfusion for intraoperative anaemia as primary reason, and not for cardiovascular instability (in this case refers to section 5). The Hb level that has triggered the transfusion will be reported.

NECTARINE: NEonate – Children STudy of Anaesthesia pRactice IN Europe

Epidemiology of critical events, morbidity and mortality in neonatal anaesthesia:
A European prospective multicentre observational study

PROTOCOL ID: NECTARINE

ClinicalTrials.gov identifier # NCT02350348

Statistical Analysis Plan (SAP) of Final Analysis

Final Version: V1.0 - 5 August 2019

1. Preface

The NECTARINE Study is being completed to assess the occurrence of clinical interventions in neonates and infants undergoing anesthesia for surgical or diagnostic procedures and their outcome in terms of morbidity and mortality.

In fact, the occurrence of critical events and/or severe physiological derangements during anaesthesia and the need for a specific intervention can be affected by many predicted and unpredicted factors: the clinical condition of the child; the type of surgical procedure; and the overall anaesthesia management. For these reasons it was relevant to collect data from a broad neonatal population undergoing anaesthesia across multiple European Centres undertaking neonatal anaesthesia.
The study aims were: (i) to identify the type and frequency of treatments used to correct perioperative critical events; (ii) the clinical event and/or threshold of physiological parameters that triggered an intervention; and (iii) collect data from medical records (or parental questionnaire at 90 days) related to 30 and 90-day morbidity and mortality after anaesthesia.

The following documents were reviewed in preparation of this SAP:
- Clinical Research Protocol **NCT02350348**, v1.0, approved in date 28 August 2015
- Case report form (CRF) v1.1 approved on 19th October 2015
- The cleaning plan approved on 13th October 2017

2. SAP Purpose

This document describes the proposed statistical analysis for the NECTARINE study. The purpose is:
1. to outline the planned analyses to be completed to support the completion of the Clinical Study Report. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts.
2. to avoid any misleading interferences that would arise from post-hoc analyses. Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP performed will be clearly identified in the respective CSR.
3. **Study objectives and endpoints**

3.1 Primary objective: To determine the incidence of peri-anaesthetic intervention(s) and/or medical treatment(s) performed in response to a potentially life-threatening critical event or to correct major deviations in physiological parameters.

3.2 Secondary objectives:

i) To investigate the occurrence of adverse events in the immediate postoperative period (up to 120 minutes after anaesthesia) and evaluate links with intraoperative critical events.
j) To investigate predictive factors for life-threatening critical events.
k) To investigate potential predictive factors for significant deviations in physiological parameters.
l) To determine mortality within 30 days after anaesthesia.
m) To determine morbidity at 30 days after anaesthesia (if still in hospital), or until hospital discharge, based on the medical record.
n) To report mortality at 90 days after anaesthesia via hospital records or parental questionnaire.
o) To evaluate associations between critical events and increased morbidity and mortality.
p) To describe the differences in neonatal anaesthesia practice throughout Europe.

3.3 Primary target variable:

The primary targeted variable is the occurrence or not of peri-anaesthetic intervention(s) and/or medical treatment(s) performed in response to a potentially life-threatening critical event or to correct major deviations in physiological parameters among a list of pre-determined of treatments and/or monitor derangements:

9. Airway management;
10. Peripheral oxygen saturation (SpO_2) and/or arterial oxygen saturation (SaO_2);
11. End-tidal carbon dioxide (CO_2) (and/or arterial or venous CO_2);
12. Glycaemia, and Na^+;
13. Cardiovascular instability: blood pressure, heart rate;
14. Body temperature;
15. Brain oxygenation by NIRS (if available);
16. Haemoglobin level.

When an intervention was performed in response to a physiological derangement, the clinical condition and/or the monitored parameter that triggered the intervention must have been reported. A descriptive analysis of all the interventions and their triggers will be performed.

3.4 Secondary targeted variables:

- Demographic data and patients' characteristics.
- Number of previous anaesthesia events.
- Co-morbidities.
- Baseline physiological parameters.
- Duration and type of surgery.
- Type of intervention(s) and relative trigger.
- Outcome generated by the intervention.
- The incidence of adverse events up to the first 120 minutes after anaesthesia.

- In-hospital mortality up to 30 days after anaesthesia as determined from medical records.
- Status at 30 days from anaesthesia and any morbidity at 30 days after anaesthesia as determined from medical records: until discharge or at 30 days if still in hospital.
- **Any NICU/PICU admission/re-admission during the 30 days after anaesthesia.**
- **Any morbidity event during the 30 days after anaesthesia.**
- In- and out-hospital mortality and morbidity at 90 days after anaesthesia.
- Status at 90 days:
    - Alive – discharged
    - Alive – still in hospital
    - Deceased.

4. Overall study plan and selection of study population

Neonates and young infants are at increased risk of perioperative adverse events that may be associated with prolonged hospital stay, unplanned intensive care admission, and worse outcome; all of which can have a considerable impact on the overall quality of life and cost of care. Several multicentre studies explored the incidence of severe critical event during anaesthesia in children, including also neonates and infants. However, extrapolating data from a broad population of patients is a complex exercise. For example, the recently published Clinical Trial Network study APRICOT reported the incidence of severe critical events in neonates and infants, but the definition of critical events and the generalizability to the neonatal population are not straightforward. Factors that limit the ability to directly extrapolate data from older children to neonates and infants are:

5. The range of normal physiological parameters for term and preterm babies under general anaesthesia are not validated.
6. The need for intervention in case of out-of-range parameters is not clearly defined and there is no clinical evidence yet that a specific clinical or pharmacological intervention may result in a better outcome.
7. Neonates undergoing general anaesthesia for diagnostic or surgical procedures frequently have multiple co-morbidities (such as extreme prematurity, congenital malformations, congenital heart disease etc.), which may further increase morbidity and mortality.
8. Neonates and infants are particularly vulnerable patients, with an increased anaesthetic risk and higher perioperative morbidity and mortality. Last, the lack of validated and universally accepted "normal" ranges of physiological parameters under general anaesthesia, makes it difficult to develop standardised treatment protocols that aim to minimise negative outcomes.

The study population included in the Nectarine study was formed by neonates and infants from birth to 60 weeks of post-menstrual age (PMA), scheduled for an elective, emergency or urgent diagnostic or surgical procedure, (both cardiac and non-cardiac), under general anaesthesia with or without regional analgesia, or under regional anaesthesia alone. Patients from 61 weeks of PMA were excluded per protocol.

5. Study method

NECTARINE was a prospective, observational, multi–centre cohort study, which only included objective data collected as part of routine anaesthetic care. The only extra assessment was the telephone call for those patients discharged from the hospital. For this reason, a consent form was

signed by parents/caregivers to allow the 90-day telephone call. Some patients that refused the 90-day follow-up were not reached and then considered lost to follow-up.

Recruitment occurred for 90 days in each participating centre, day and night, weekends included. Windows of recruitment were divided into four time period of the year and each centre started recruitment and follow-up according to their local preference. Follow-up continued after the 3 months of recruitment for the following 3 months to allow competition of follow-up (as for secondary endpoint).

Sample size calculation

The primary end-point of the NECTARINE study is to evaluate the incidence of medical interventions for life threatening conditions or critical events (as reported in section IX) in neonates and infants (aged ≤60 weeks of PMA) who had undergone general and/or regional anaesthesia.

A secondary aim of the study is to identify the potential predictors of critical events and poor outcomes (morbidity and mortality); since this requires a minimum number of events to be observed, this number has been estimated first as described below.

A total of **5,000** patients are expected to be enrolled in the present study based on the fact that a minimum number of **462** events is required in order to analyse the data through multivariate regression analysis models for the identification of the potential predictors of poor outcomes.

In fact, the number of **462** patients was obtained considering the following:

- According to the formulation n. 2 cited in Hsieh (1998), that allows for the calculation of the minimum sample needed for a logistic regression analysis with only 1 covariate, a minimum number of 776 patients (388 cases + 388 controls) is required assuming that: P1=0.4 [P1=pr(diseased|X=0)], P2=0.5 [P2=pr(diseased|X=1)], B=0.5 (B=the proportion of the sample with X=1), alpha=0.05 (alpha=Type 1 error), and power=0.80 (power=power for testing if the Odds Ratio is equal to one). This calculation was performed with the software "R", release 3.1.3 (The R foundation for Statistical Computing) using the function "SSizeLogisticBin".

- According to the same author Hsieh (1998), the previous number of 776 patients had to be corrected in order to take into account the fact that there would be more than 1 covariate in the model. The correction consisted of multiplying the previously obtained number of 776 by the Variance Inflation Factor [VIF= $1/(1\text{-rho}^2)$], where rho^2 is the multiple Correlation Coefficient relating X_1 with $X_2,\ldots.X_p$. Assuming that rho is equal to 0.4, a total number of **924** patients will be required for the "fitting" of the multivariate logistic regression models (corresponding to **462** cases + 462 controls).

- Considering that the expected percentage of events is approximately 11%, **4,200** patients are the minimum required in order to obtain 462 cases. However, taking a drop-out rate of 15% (p_{DO}=0.15), into account, **4,941** patients is the exact number required for the study, obtained with the following formula: $N_{DO}=N/(1\text{-}p_{DO})$ and, in sensibly rounding up this figure, we arrive at **5,000**.

- The estimate of the expected percentage of events was approximately 11%. This estimate was based on the results from the "APRICOT" study.

Primary statistical analysis

Descriptive analysis of the entire cohort of patients will be performed first. Patients characteristics will be provided with categorical data summarised in terms of absolute frequencies and percentages, quantitative variables summarised in terms of means and Standard Deviations (SD) in the case of normally distributed data and in terms of medians with 1^{st} and 3^{rd} quartiles (1^{st} – 3^{rd} q), or minimum and maximum values (min-max) in the case of skewed distributed data. The normality of the distributions will be evaluated by the Shapiro-Wilk test.

The incidence for the occurrence of the primary end-point (number of interventions or critical events) will be reported as a frequency and 95% Binomial Exact Confidence Intervals. Critical events and interventions will be categorized by groups according to the study definitions. Using each physiological variable that triggered intervention as a continuous variable, a ROC analysis will be performed to identify the threshold for intervention.

The associations between categorical data will be evaluated by the Chi-square test or by the Fisher's Exact test in the case of expected frequencies less than 5. The relationship between quantitative variables and the outcome (poor outcome: yes/no) will be evaluated by the Student's or Welch's *t* test or the Mann-Whitney U test in the case of skewed distributed variables or homoschedasticity assumption not being fulfilled. The relationships between quantitative variables and categorical polynomial variables will be evaluated by the Analysis of Variance (F test), or by the non-parametric analysis of variance (Kruskal-Wallis test). In order to avoid the "multiple comparison error", the Scheffé test will be used as *a posterior* test or the Bonferroni's correction will be applied. In the latter case, the P value will be reported as "P_B".

All the tests will be two-sided and a P value < 0.05 will be considered as "statistically significant".

In the case of repeated observations of the same patient, generalized linear mixed models will be fitted to adjust for correlated observations using the binomial distribution for binary response variables, the Poisson distribution for counts, the negative binomial or quasi-Poisson distribution for over-dispersed counts, and the normal distribution for continuous dependent variables.

Multiple relative risk regression models will be fitted in order to identify the potential risk factors that are associated with the various endpoints. Variables that were statistically associated with the outcome at the bivariate analysis or clinically relevant variables will be entered into the model. Variance inflation factors will be calculated to assess multicollinearity. We will consider collapsing some correlated binary or dichotomised categorical variables into one variable using the OR logical operator and excluding some of the highly correlated continuous variables. The log-Likelihood Ratio (LR) test will be used to test the relevance of each variable in the model. Adjusted Odds Ratios with their 95% Confidence Intervals (95% CI) will also be calculated and reported and the Area under ROC Curve of the model will be used as a measure of the goodness-of-fit of the logistic regression model.

Adjusted Relative Risks (RR_{Adj}) with their 95% Confidence Intervals (95% CI) will also be calculated and reported for the Poisson Regression model.

Multivariable analyses will be also carried out via generalized linear mixed models taking the participating centre as a random factor.

Secondary analysis:

Exploratory clinical outcomes or ancillary analysis will be performed to provide valuable information about the cohort such as those related to the airway and anaesthesia management, ventilation strategies, use of opioids, inotropes etc. Also number of children included by participating center during the study period will be compared with the occurrence of events and patients' outcome to explore potential influence and/or correlation

In addition, a subgroup analysis on patients undergoing congenital heart surgery is planned.

Institutions/countries can request data extraction for further analysis and quality improvement projects. Extraction of database subsets must be approved by the Steering Committee.

Handling of missing data:

Since the primary outcome is the incidence of peri-anaesthetic intervention(s) and/or medical treatment(s) performed in response to a potentially life-threatening critical event or to correct major deviations in physiological parameters. We predict a small number of missing values. However, if there are missing variables among the data collected particularly those related to the secondary outcome, we will drop the missing cases if the number is less than 5%. For the linear regression analysis, if the number of missing data is high, we will drop these cases from the analysis and we will perform a statistical imputation of the missing data (propensity score method) and subsequently we will compare the results obtained with or without data imputation.

Software:

The software "Statistica", release 9 (StatSoft Inc., Tulsa, OK, USA) will be used for all univariate and bivariate analyses and the software "Stata", release 11.0 (StataCorp, College Station, TX, USA), the R environment, version 3.6.0 (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria), or the software SPSS, version 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.) will be used for all the multivariate analyses.