Health and developmental outcomes of low-birth-weight infants born at the Centre de Référence d'Urgences Obstétricales (CRUO), Port-au-Prince, Haiti.

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Full title

A prospective cohort study investigating health and developmental outcomes of low birth weight infants born at the Centre de Reference d'Urgences Obstétricales (CRUO), Port-au-Prince, Haiti.

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Funding and conflicts of interest

Médecins Sans Frontières Netherlands (MSF-OCA) funded the research. No external funding was sought. No members of the study team report to have any conflicts of interest.

Summary

Title

A prospective cohort study investigating health and developmental outcomes of low birth weight infants born at the Centre de Reference d'Urgences Obstretricales (CRUO), Port-au-Prince, Haiti.

Primary objective: To describe and compare health and developmental outcomes between low birthweight (LBW) and normal weight infants up to 24 ~~18~~ months post-partum, corrected for gestational age.

Secondary objective

To identify risk factors associated with negative health and developmental outcomes in LBW infants.

Method

Design: The study is a prospective cohort study of 593 infants born in CRUO hospital. The participants are followed up from birth and post discharge at 3, 6, 12, 15, 18, 21 and 24 ~~and 18~~ months corrected for gestational age.

Outcome measures:

- Mortality during hospitalisation and post discharge;
- Changes in weight and height during hospitalisation and post discharge;
- Morbidity during hospitalisation: sepsis, NEC, periods of hypoxia due to either pulmonary disease or episodes of apnoea, jaundice and episodes of hypoglycaemia and seizures;
- Morbidity post discharge: vaccine preventable disease, other severe morbidities;
- Motor assessment (Fine and Gross) done at 6 month corrected gestational age as measured by the Bayley scale III (BSIDIII);
- Motor assessment (fine and Gross), Cognitive assessment and Language assessment (receptive and communicative) done at 12, ~~and~~ 18 and 24 months corrected gestational age
- Gross hearing impairment at ~~,~~ 6, 12, ~~and~~ 18 and 24 months corrected for gestational age as measured by the BSID III;
- Gross visual impairment ~~at 6~~at 6, 12, 18 and 24 ~~and 18~~ months corrected for gestational age as measured by the BSID III;

Ethical considerations

This component of the study will start once ethical approval from the MSF Ethics Review Board (ERB) and the Comité National de Bioéthique in Haiti are obtained.

Abbreviations

MSF	Médecins Sans Frontières
CRUO	Centre de Référence d'Urgences Obstétricales
KMC	Kangaroo Mother Care
MSPP	Ministère de la Santé Publique et de la Population.
GA	Gestational Age
OPD	Outpatient Department
LBW	Low Birth Weight.
ELBW	Extremely Low Birth Weight
VLBW	Very Low Birth Weight
CEMONC	Comprehensive, Emergency Obstetric and Neonatal Care
CPAP	Continuous Positive Airway Pressure
NEC	Necrotising EnteroColitis
BSIDIII	Bayley Scales of Infant Development III

Contents

1 Introduction

The World Health Organization (WHO) defines prematurity as birth before 37 completed weeks of pregnancy [1]. In resource-limited countries it can be difficult to establish the gestational age of a neonate and therefore the birth weight is often used as a marker of its maturity. Low Birth Weight (LBW) neonates are defined as weighing less than 2500 grams. The LBW can be caused by either prematurity or intrauterine growth retardation (Small for Gestational Age or SGA). Also preterm neonates can have a weight appropriate for their gestational age (AGA) or a weight lower than normal for gestation (SGA).

1.1 Mortality

It is important to realise that the terms premature and LBW cannot be simply used interchangeably because they are not the same and mortality risk ratios associated with SGA are overall smaller than in preterm. The mortality of neonates increases dramatically in preterm infants compared to full term infants. The median neonatal mortality rate (per 1000 live births) of infants that are full-term and ~~AGA and~~AGA and full-term and SGA is 2.4-8.4 and 10.1-17.6 respectively [2]. Comparatively, infants that are preterm and AGA have a median mortality rate of 23.5-53.0 per 1000 live births and the median mortality in preterm and SGA infants ~~is 70~~is 70.2-106.6 per 1000 live births [2].

Mortality caused by premature or SGA birth is not restricted to the neonatal period. In order to better understand the influence of prematurity or foetal growth restriction on mortality we should look beyond this period within the first year of life. Being born preterm also increases an infant's risk of dying due to other causes, especially from infections [3], with preterm birth estimated to be a risk factor in at least 50% of all neonatal deaths [4].

1.2 Risk factors for negative outcomes in low birth weight infants

Morbidity and long term sequelae in infants increase with decreasing GA and/or weight. In high-resource settings, studies show that survival without major morbidities increase from 32% at 23 weeks to 91% at 31 weeks of gestational age [5]. However, also in the late preterm infants (34-37 weeks of GA) there continues to be a concern about increased long term morbidity [6].

Impairment resulting from prematurity or LBW can be either physical (e.g. respiratory complaints, growth restriction, gastrointestinal problems) or developmental (motor or cognitive development). Being premature and/or SGA has a marked effect on the developmental outcome but neonatal complications (e.g. sepsis, necrotizing enterocolitis (NEC), intraventricular haemorrhage, jaundice etc.) may have an even larger detrimental effect on the long term cognitive development of the individual as was shown in a study of a university psychological department in the UK [7].

Risk factors for negative outcomes (mortality or other morbidities) in newborns and infants can be classified into the following categories: maternal morbidities, infant morbidities and treatment modalities. The major factors contributing to these categories are described below:

a) Maternal morbidities and drug consumption

Maternal intrapartum fever has been shown to be associated with neonatal sepsis, which in turn can lead to adverse neurodevelopmental outcomes [8–10] (see below). Also, severe underlying maternal morbidities such as diabetes, asthma or HIV infections have been shown to cause pathologies in neonates including prematurity, low birth weight and infant death [11–15]. Hypertension and eclampsia are both strongly associated with low birth weight and prematurity in neonates [12,15–17].; can lead with heart and neurological illness. Additionally, it is known that

consumption of alcohol and tobacco containing products with regularity during the pregnancy has led to poorer neurodevelopmental outcomes in infants [18]. Further, other medications taken during pregnancy (i.e. ibuprofen and misoprostol) have resulted in poor neurodevelopmental outcomes in children [19–21].

b) Infant Morbidities:

Neonatal sepsis has been shown to be related to adverse neurodevelopmental outcomes. A recent study showed an adjusted odds ratio for adverse neurodevelopmental outcomes using the Bayley Scale of 4.8 and 3.2 in gram negative and *Candida* sepsis respectively compared to uncomplicated controls [10]. A French study [22] showed that the risk of cerebral palsy increased in premature infants (22-32 weeks of GA) with sepsis compared to those without sepsis. The Odds Ratio (OR) for cerebral palsy with early onset of sepsis was 1.70 (95%CI 0.84-3.45) and that for cerebral palsy with late onset of sepsis was 1.71 (95% CI 1.14-2.56); for both combined the OR was 2.33 (95% CI 1.02-5.53). Also work from Brazil showed that 68.8% of neonates who had sepsis (confirmed by culture) had a delay in motor skill development compared to 29.3% of neonates who never had an episode of sepsis [23].

Another common morbidity in premature infants is necrotizing enterocolitis (NEC) and it has been shown to predispose the infant to neurodevelopmental delay [24,25]. This might be caused either by the severity of the infection and associated illness or by the possible bacteraemia in NEC. NEC requiring surgery will cause increased sequelae compared to NEC that is treatable in a more conservative manner [26].

Immaturity in infants also contributes to hyaline membrane disease and apnea. ~~Therefore~~Therefore, establishing a clear/direct relationship between these morbidities and neurodevelopmental delay is difficult, as the immaturity of the infant might be confounding the condition. However, one study has shown that hyaline membrane disease by itself has an effect on the neurodevelopmental outcome at the age of 4 months but that this effect disappears at later stages [27]. Moreover, prolonged repetitive apnea's also might cause cerebral hypoxia (see below) and which is why giving caffeine to premature infants has shown to have a beneficial effect on long-term developmental outcome [28].

There is ample evidence that perinatal asphyxia causing hypoxic ischaemic encephalopathy can result in serious neurodevelopmental delay, which is directly associated with the severity of the asphyxia [29,30]. Also intrauterine and neonatal insults of variable origin, which include hypoxic ischemia, have been shown to have an overall median risk of at least one neurodevelopmental sequela as high as 39% [11].

Hypoglycaemia is a common occurrence in premature infants. It has been shown that the number of days on which moderate hypoglycaemia (< 2.6 mmol/l = 45 mg/dl) occurred are associated with reduced mental and motor development scores at 18 months corrected for gestational age [31].

c) Treatment modalities:

Several treatment modalities which have been commonly employed in premature infants have been shown to have a negative impact. Firstly, oxygen administration is known to cause Retinopathy of Prematurity (ROP) and therefore might cause considerable harm to the infant [32]. Secondly the use of aminoglycosides (like

gentamycin) has been shown to have the potential of causing auditory toxicity, if levels (maximum as well as trough levels) are too high. In resource limited settings (such as the maternity hospital in Port au Prince, Haiti, run by MSF-OCA), protocols usually include a one day dosing system with a generally accepted gentamycin dose [33]. However, these facilities do not have the ability to test gentamycin levels in infants and therefore precise measurements on gentamycin dosing are absent, potentially leading to gentamycin being given for too long, too frequently or in the wrong dose.

1.3 Evidence-based interventions that positively influence neonatal mortality

There are several packages of interventions or individual interventions that have been proven effective in reducing neonatal morbidity and mortality in resource-limited countries [34]. Although studies on their impact on neurodevelopmental outcomes in these countries are absent, they are assumed to positively influence complications such as sepsis, respiratory diseases, asphyxia, hypothermia and others. Therefore they are also assumed to positively influence neurodevelopmental outcome.

The most important interventions are:

a) **Antenatal**: infection prevention or treatment and tetanus vaccination in the mothers; A Swiss study related favourable neurodevelopmental outcome (measured by Bayley Scale II, BSID II) to a completed course of antenatal steroids (41%) compared to no or an incomplete course (28%) [35].

b) **Intrapartum**: infection prevention and treatment in the mothers and corticosteroids for lung maturation in the foetus [36,37];

c) **Postpartum**: neonatal resuscitation [38], clean cord care [39–41] and the positive effect of Kangaroo Mother Care (KMC) on neonatal mortality has been described and includes positive effects on the family environment and the infant's cognitive development [42,43].

1.4 MSF activities in Haiti for neonates

MSF has a long history of obstetric hospitals in Port au Prince, starting in 2006 with no admission criteria at the Jude Anne hospital. This was followed by introduction of admission criteria to focus on high risk deliveries when activities were moved to the Solidarité hospital which was later damaged in the January 2010 earthquake. Post-earthquake the team temporarily supported the state maternity hospital, Isaie Jeanty until the opening of the current structure, CRUO, in March 2011. CRUO is a unique obstetrical structure for MSF as it deals mainly with obstetrical emergencies. The bulk of the admissions (40% in 2012) were for eclampsia and pre-eclampsia which are conditions that often lead to premature and LBW infants being born. In recent years, the programme has expanded and our neonatal admission rate is high with a 2013 average of 182 monthly admissions. On average 55.3% of neonatal admissions are < 2.5kg (13.6% < 1.25kg) and 46.3% of admissions are < 36 weeks gestation (5.9% <29 weeks).

At this moment the treatment modalities for neonates include nasal Continuous Positive Airway Pressure (CPAP), oxygen, caffeine, IV fluids, antibiotics, anticonvulsants, incubator care and KMC (the last since June 2012). When the KMC was started, an ambulatory follow-up of discharged infants until they reach 40 weeks of gestational age and 2kg was also initiated.

2. Study rationale

In 2013, 78% of LBW infants (<2500g) admitted to CRUO neonatology survived to discharge. This group included a high proportion of infants that were premature and/or had other medical conditions in addition to the LBW. Each month 15-30 LBW infants are discharged from ambulatory KMC. The mean weight at the start of inpatient KMC is 1359g with a mean gestational age of 34 weeks. The mean discharge weight from ambulatory KMC is 2490g at a mean gestational age of 40.6 weeks. This year, none of these infants have had obvious neurological abnormalities on general examination at discharge.

~~However~~However, we have no information on the longer term outcomes of these discharged LBW infants with respect to their mortality, morbidity and development. In published literature there is also a lack of data on longer term follow-up of infant's post-hospitalisation in resource-limited settings. Moreover, we have no understanding whether our current treatments in CRUO are always in the best interest of the infant on the longer term and keeping very young, small neonates alive might actually cause long term serious physical, emotional or developmental harm. The absence of evidence for best practice in medical care of LBW neonates to improve short and longer term outcomes does not facilitate this understanding.

It is in this context that we propose to conduct this study on short and longer term outcomes in infants born in CRUO with LBW. We intend to use the Bayley Scale (BSIDIII) for measuring the neurodevelopmental outcomes in infants. As the scale has not been validated in the Haitian context we are required to include a comparison group of normal birth weight infants to compare the LBW infants to. Therefore, we will be including all babies born in CRUO into the cohort. While this will not constitute a formal evaluation of the BSIDIII in this context, it will give us a comparison group of babies who are not LBW.

We hope that by documenting and analysing the short term outcomes of these ~~infants during~~infants during their hospitalisation and longer term outcomes after discharge we will add to existing data on this topic, but also that we might identify risk factors that are directly associated with negative outcomes. With this information we will be in a better position to take more adequate medical decisions in the treatment of LBW neonates at CRUO. Examples of this decision making could be in the implementation of gentamycin peak and through monitoring or adaptations of resuscitation guidelines that are linked to the evidence of long term morbidity and mortality. A more positive example of this would be the identification of which LBW babies eventually flourish and identify which treatment options/factors may have contributed to this outcome. Ultimately, we want to assure that babies not only exit our facility but exit with a reasonable chance of long term survival and quality of life and want to tailor our medical care to this.
~~Additionally~~Additionally, we might be able communicate better with parents on the prognosis of their children as well as managing their short and long term expectations. Ultimately the data collected could be used to improve the care in other non-MSF health facilities in low-resource-settings that deal with this same target group of neonates.

2 Objectives

Primary objective:
To describe and compare health and developmental outcomes between LBW and normal weight infants up to 24 ~~18~~ months post-partum, corrected for gestation age.

Secondary objective
To identify risk factors associated with negative health and developmental outcomes in LBW infants.

3 General study design

The study will be a prospective cohort study of infants born in CRUO hospital. The participants will be followed up from birth and post discharge at 3, 6, 12, 15, 18, 21 and 24 months ~~and 18 months~~ corrected for gestational age.

The study will start once ethical approval from the MSF Ethics Review Board (ERB) and the Comité National de Bioéthique in Haiti are obtained.

4 Outcome measures

The prospective cohort will be followed from birth to 3, 6, 12, 15, 18, 21 and 24 ~~and 18~~ months after birth (corrected for gestational age) and the incidence of the following outcomes in all babies will be captured:

- Mortality during hospitalisation and post discharge;
- Changes in weight and height during hospitalisation and post discharge;
- Morbidity during hospitalisation: sepsis, NEC, periods of hypoxia due to either pulmonary disease or episodes of apnoea, jaundice and episodes of hypoglycaemia and seizures;
- Morbidity post discharge: vaccine preventable disease, other severe morbidities;
- Motor assessment (Fine and Gross) done at 6 month corrected gestational age as measured by the Bayley scale III (BSIDIII);
- Motor assessment (fine and Gross), Cognitive assessment and Language assessment (receptive and communicative) done at 12, ~~and~~ 18 and 24 months corrected gestational age
- Gross hearing impairment ~~at ,~~at, 6, 12, 18 and 24 ~~and 18~~ months corrected for gestational age as measured by the BSID III;
- Gross visual impairment ~~at 6~~at 6, 12, 18 and 24 ~~and 18~~ months corrected for gestational age as measured by the BSID III;

5 Risk factors

The main risk factors that we expect to be associated with negative short and longer term outcomes will be infants that had a very low gestational ages at birth (<34 weeks at gestation age) and infants born with LBW (<2500g).

The other risk factors which we expect to encounter to be associated with negative outcomes and which we will try and analyse from the study data can be classified as maternal risk factors, morbidities and treatment modalities:

a) Maternal morbidities: maternal fever, maternal underlying severe morbidities such as hypertension and eclampsia occurrence, the use of drugs during pregnancy (self-medication)

b) Infant ~~morbidities :~~morbidities: sepsis, NEC, pulmonary disease and apnoea, Hypoxic Ischaemic Encephalopathy and convulsions and hypoglycaemia;

c) Treatment modalities: administration of oxygen and gentamycin;

d) Use of other substances (ibuprofen, tobacco use, alcohol and misoprostol) during the pregnancy

6 Study site

6.1 Study settings

The study will take place in the Out Patient Department (OPD) structure of the CRUO in Port-au-Prince, Haiti.

6.2 Participants

6.2.1 Study population

We will draw the study sample from all infants that are born in CRUO. This will include:

- Infants born in CRUO and admitted to neonatology.
- Infants born in CRUO but not admitted to neonatology.
- Infants born in CRUO that die before discharge.

6.2.2 Inclusion and exclusion criteria:

All infants born in CRUO will be eligible for inclusion into the study. Exclusion criteria in the study will be:

- Any major, obvious congenital malformations (e.g.: obvious syndromes, diaphragmatic hernias, gastroschizis, anal atresia, spina~~l~~ bifida.);
- Infants that are abandoned by parents;
- Any discharged patients whose parents refuse to sign the consent form (these infants will still be included in the analysis for the outcomes during the period of hospitalisation).

6.2.3 Withdrawal:

Consent to participate in the follow-up study can be withdrawn at any point into the study and the infant/parent will not suffer any negative implications from this. Even if the parent chooses to remove the infant from the study, the infant can continue to be seen for follow-up and receive the same benefits that a child in the study would.

7 Participant selection and enrolment

7.1 Identifying participants for the cohort

Every neonate born in CRUO will be considered for inclusion into the study. The national Principal Investigator with the expat paediatrician will identify infants that meet the inclusion criteria.

7.2 Consenting participants

During the period of hospitalisation all data to be collected and documented will be based on the collected medical data at CRUO which forms part of the routine procedures for all admitted patients. As such, no consent will be asked to parents to analyse these data as part of the study, as it will be analysed retrospectively as routine medical data.

We will only seek to obtain informed consent for the infants in the cohort that are discharged from CRUO and who will continue to participate in the follow-up component of the study. As these infants are not in a position to consent or assent to participate in the study we will rely on the presence and informed consent of the legal guardian.

In Haiti the mother is considered the legal guardian at 18 years of age. If the mother is under 18 years, but the father is 18 years or older, consent can be given by the father. If the mother is younger than 18 years and no father is present or the father is younger than 18 years then the mother's parents have the power to give consent.

Prior to consent, the information given to each patient will cover the study rationale, objectives, duration and possible implications for the participant and caretaker. This information will be given verbally and in writing in either French or Creole depending on the preference of the person. Implications include the benefits and risks of the study, which will be clearly explained. Any question related to study involvement will be answered. The legal guardian will understand that they have a choice over whether they participate in the study and that refusal to participate in the study will not affect their access to the standard of medical care given to all infants born in CRUO. The consent form will be read aloud, and, if agreed, signed. (See consent form Annex 1).

For infants that are admitted to neonatology, the consent process will be initiated as soon as the parents are present and the mother (or legal guardian) is well enough to give informed consent. For well-infants who do not pass through paediatrics the discussion will begin as soon as possible after birth as the mother's tend to only stay in hospital 24-48 hours.

7.3 Consent at 12 months

At 12 months we will start collecting additional maternal data and request that mothers to return for a further 2 follow up visits (pending ERB approval). As this deviates from the original consent and given that, in particular, the request for maternal data is sensitive, we will re-do consent for both mothers and babies. The consent at this time will cover a clear explanation of the reasons why we would like to extend the study and ask further information. This consent will be done with two signatures as it is possible that the mother (legal guardian) will consent to one part and not the other.

7.4 Ineligible and un-recruited participants

Infants who do not meet inclusion criteria or who are ineligible for the study will receive the standard of care offered to all infants born in CRUO including medical care (including referral to other healthcare facilities if deemed medically necessary), KMC and OPD if applicable.

8 Study and Clinical procedures

8.1 General

The study will follow as much as possible the services offered in any general paediatric practice in Haiti. Infants enrolled in the study will be requested to return for follow-up visits at 3, 6, 12, 15 and 18 months corrected gestational age.

Table 1 summarises the medical information and variables which will be collected for infants in the cohort.

Table 1: Summary of variables assessed at all stages of the infant outcome study, CRUO, Port-au-Prince.

		Discharged					
	During Hospitalisation	Upon discharge	3 month F/U	6 month F/U	12 month F/U	15 month F/U	18 month F/U
	Admission to Study (during hospitalisation)		F/U#1	F/U#2	F/U#3	F/U#4	F/U#5
Routine medical data during admission	X						
Consent form 1		X					
Consent form 2					X		
Full general physical exam			X	X	X	X	X
Catch up and/or orient PEV			X	X	X	X	X
Weight and length			X	X	X	X	X
Mortality			X	X	X	X	X
Full Neurologic exam				X	X		X
Bayley assessment including Fine and Gross motor developement				X	X		X
Bayley assessment including Fine/gross motor; cognitive and language (expressive and receptive)				X	X		X
Gross hearing/Vision test (as part of Bayley scale)				X	X		X

	Hospitalization	Post hospitalization							
		Discharge	3 Months F/U	6 Months F/U	12 months FU	15 months F/U	18 months F/U	21 months F/U	24 months F/U
	Admission to study (during hospitalization)		F/U#1	F/U#2	F/U#3	F/U#4	F/U#5	F/U#6	F/u#7
Routine medical data during admission	X								
Consent form 1	X								
Consent form 2					X				
Consent form 3							X		
Full general physical exam		X	X	X	X	X	X	X	X
Catch up and/or orient for PEV			X	X	X	X	X	X	X
Weight and length		X	X	X	X	X	X	X	X
Mortality		X	X	X	X	X	X	X	X
Neuro exam				X	X		X		X
Bayley III exam Motor development				X	X		X		X
Bayley III exam Motor, Cognitive and Language				X	X		X		X
Gross hearing/Vision test (as part of BayleyIII)				X	X		X		X

8.2 Procedures and data collection during hospitalisation

Patients admitted to the study already have a patient file from CRUO which includes an in-depth account of their birth history and hospitalization as well as their medical status at exit. Data currently being collected as part of the paediatric programme that will be used for the study includes: (See Annex 4)

- Maternal diagnosis and relevant medication (e.g. maternal infections, steroids for lung maturation).
- Apgar score: a clinical scoring system that measures the colour, tone, respiratory effort, heart rate and reflexes using a 0 – ~~2 point~~2-point scale for each criterion giving a total out of 10. It is measured at 1, 5 and 10 minutes of life. The Apgar score is used to assess the ease of transition to extra uterine life, and the response to resuscitation if needed.
- Resuscitation at birth, weight at birth, gestational age at birth estimated clinically using the Ballard score.
    - In CRUO, resuscitation includes: giving inflation breaths and bag and mask ~~ventilation ,~~ventilation, with oxygen if clinically appropriate; chest compressions; umbilical vein catheterisation if needed; IV fluid boluses of 10% glucose and 0.9% Sodium chloride as clinically indicated; intubation and endotracheal suction only in the case of meconium aspiration, though not for the purposes of ventilation; adrenaline.
    - A sliding scale of resuscitation intervention is used according to the weight and estimated gestation age of the infant in order to not to do harm keeping the extremely small and premature without a realistic chance alive and to prioritise limited resources. This is detailed in ANNEX 8
- Diagnosis on admission.
    - Hypothermic on admission (<35.5C axillary)
    - Hypoxic on admission
    - Shock on admission (capillary refill time >2secs or given bolus)
    - Hypoglycaemia on admission (< 45 g/dl)
    - Sepsis (suspected/manifest maternal-foetal infection, based on clinical judgement and existing risk factors)
    - Asphyxia (Apgar score < 6 at 5 ~~minutes~~minutes' post-partum)
    - LBW (< 2500 g)
    - Estimated gestational age
- Episode of NEC (Defined as: green residue/ abdominal distension/ instability)
    - NEC is a gastrointestinal disease of infants, occurring much more commonly in premature and LBW infants. There is a combination of gut ischaemia leading to gastrointestinal haemorrhage and ulceration, and bacterial infection. It usually presents in the 2nd-3rd week of life. Signs can initially be non-specific, such as temperature instability or hypoglycaemia, but can progress to include gastrointestinal bleeding, bilious gastric aspirates, abdominal distention, bowel perforation and shock.
- Episodes of clinical sepsis
- Episodes of Apnea
- Episodes of hypoglycaemia
- Episodes of Seizure activity
- Treatments received:
    - CPAP is a form of respiratory support commonly used in neonatology. It is used for diseases such as hyaline membrane disease, pneumonia and sepsis with respiratory difficulties. CPAP provides a positive end expiratory pressure that assists in recruitment of alveoli and helps to prevent airway collapse. It can only be used if the infant is breathing spontaneously.
    - Phototherapy, highest bilirubin measurement.

- Transfusion
- Length of time of antibiotics in total
- Oxygen therapy, duration
- Caffeine therapy and duration.
- Length of hospitalization

8.3 Procedures and data collection at discharge from CRUO

For those infants for whom consent is given upon discharge to continue in the follow-up component of the study, the following clinical parameters and information will be collected at the time of discharge:

- Consent form for follow-up in the cohort;
- Weight and Length;
- Outcome at discharge, this includes a general physical exam, a neurological exam (reflexes, power, tone) and information on any obvious impairments.

8.4 Follow up visits

8.4.1.1 Follow-up Visit: At 3 months corrected gestational age.

A follow-up visit at 3 months corrected GA will be used to re-establish contact with the infants and their families. The infant will receive a physical examination and medical care and treatment of conditions that can be managed on an outpatient basis if needed. Any condition requiring inpatient treatment will have to be referred to a local health structure. The infants will also receive a review of their vaccination status, if missing ~~vaccines~~vaccines, we will provide catch-up per national protocol and orient them to Ministère de la Santé Publique et de la Population (MSPP) locations where routine vaccinations can be received.

A review of the study and its purpose will be done to assure that the parent continues to consent.

The clinical assessment will include (see annex 6):

- History over previous period with respect to: illnesses and treatment, vaccinations, feeding difficulties.
- A full, general physical examination and treatment if necessary. As previously mentioned, our capacity for treatment will remain quite basic. We will be able to assess and treat:
  - Uncomplicated infections not necessitating hospital admission;
  - Uncomplicated Malaria;
  - Clinically suspected gastrointestinal helminthic infections;
  - Feeding difficulties (inability to latch, regurgitation);
  - Referral to paediatric medical, orthopaedic or surgical services (outside of CRUO) if required (the challenges of referrals in Haiti are further discussed in section 12.8: Potential Risks)

8.4.1.2 Follow-up visit: At 6 months corrected gestational age.

The 6 follow-up visits will include the same assessment as described at 3 months but will have the addition of the BSIDIII and a gross neurological assessment (see section 7.3 for definition).

- Bayley scale assessment: Including Gross and fine motor development.
- Gross hearing and vision tests included as part of the BSIDIII assessment.

All measurements will be done by paediatricians working in CRUO and who followed a training by a Bayley scale trainer. They will all be supervised on a regular basis by the expat paediatrician and the Primary Investigator to ensure consistency in grading using these scales.

8.4.1.3 Follow-up visit: At 15 and 21 months corrected gestational age.

A follow-up visit at 15 and ~~months~~21 months corrected GA will be used primarily to maintain a close contact with the infants and their families. The infant will receive a physical examination and medical care and treatment of conditions that can be managed on an outpatient basis if needed. Any condition requiring inpatient treatment will have to be referred to a local health structure. The infants will also receive a review of their vaccination status, if missing ~~vaccines~~vaccines, we will provide catch-up per national protocol and orient them to Ministère de la Santé Publique et de la Population (MSPP) locations where routine vaccinations can be received.

The clinical assessment will include (see annex 6):

- History over previous period with respect to: illnesses and treatment, vaccinations, feeding difficulties.
- A full, general physical examination and treatment if necessary. As previously mentioned, our capacity for treatment will remain quite basic. We will be able to assess and treat:
    - Uncomplicated infections not necessitating hospital admission;
    - Uncomplicated Malaria;
    - Clinically suspected gastrointestinal helminthic infections;
    - Feeding difficulties (inability to latch, regurgitation);
    - Referral to paediatric medical, orthopaedic or surgical services (outside of CRUO) if required (the challenges of referrals in Haiti are further discussed in section 12.8: Potential Risks)

8.4.1.4 Follow-up visits: At 12, ~~and~~ 18 and 24 months corrected gestational age.

The 12, 18 and 24 ~~and 18~~ months follow-up visits will include the same assessment as described at 3, 6 and 15 months but will have the addition of the Cognitive and Language assessments as described by the BSIDIII

- Bayley scale assessment: Motor scale (gross and fine), Cognitive scale and Language scale (expressive and receptive).
- Gross hearing and vision tests included as part of the BSIDIII assessment.
- Gross hearing and vision tests included as part of the BSIDIII assessment.

All measurements will be done by paediatricians working in CRUO. All paediatricians will be trained on the BSID. They will all be supervised on a regular basis by the expat paediatrician and the Primary Investigator to ensure consistency in grading using these scales.

~~All measurements will be done by paediatricians working in CRUO. All paediatricians will be trained on the BSID. They will all be supervised on a regular basis by the expat paediatrician and the Primary Investigator to ensure consistency in grading using these scales.~~

It is possible that severe developmental delays, severe neurological impairment, blindness or deafness are identified during these follow-up visits. We will offer the best possible medical care we have within the constraints of our programme at CRUO. However, there are extremely limited referral options and resources to address such conditions at present in Haiti.

8.4.1.5 Maternal risk factors

Between the 12 month and 24 ~~18~~ month follow up visits, pending maternal consent (see consent ANX 1.2) we will also try and collect information on the use of different non-prescribed substances during the pregnancy of the infant enrolled in the study

9 Height measurements for 3 and 6 month follow up ~~(amended January 2016)~~

In order to be able to correct previous errors in height measurements of infants at the 3-month and 6-month follow up visits, we propose to enroll 40 newborns born at CRUO in the first quarter of 2016. Twenty newborns should be normal birthweight and 20 newborns should be of <2500g birthweight. Newborns will be selected at random in the post-natal department of CRUO.

These newborns will undergo the following tests and measurements at the following time points:

1. Study enrollment/discharge from CRUO
    - Weight
    - Height
    - Well-baby check including vaccinations received verification
2. 3 ~~month~~months' gestational age follow~~ ~~up visit
    - Weight
    - Height
    - Well-baby check including vaccinations received verification
3. 6 ~~month~~months' gestational age follow~~ ~~up visit
    - Weight
    - Height
    - Well-baby check including vaccinations received verification

Parents/caretakers will be asked to consent to this process. No risks are identified for the individual infants, they will benefit from regular pediatric visits and the opportunity to update their vaccinations if required at each of the three visits.

Height measurements at the above mentioned follow up visits will be done in two ways in order to provide sufficient data for analysis. Thus each infant will be measured for their height in the 'incorrect' and 'correct' manner. The Incorrect manner will involve using a flexible measuring tape and measuring the length of the infant from the middle of the back of their head, down the back, around the buttocks and to the ankles (following the full curvature of the body). The correct manner of measuring their height will include placing the infant on a flat surface on their back and measuring the length from the top of their head to their ankles.

We propose to estimate the "correct" height by using a regression model based on measurements of the intended method regressed on height measurements based on the incorrect method and use the calculated regression line to predict the height measurements that would have been obtained using the intended method of measurement. The regression model will be evaluated for the goodness of fit and ability to predict the estimated heights to ensure the method is appropriate. A series of sensitivity analyses to understand the impact of using the estimated height measurements as well as the impact of ignoring any effect of the incorrectly measured heights.

10 Withdrawal procedures

In case of withdrawal from the study, whatever is the cause, the participant will be offered continued follow-up services as prescribed to study participants.

11 Potential confounders and effect modifiers

Many of the risk factors which we intend to study and their association to negative outcomes in infants in Haiti have the potential to function as potential confounders and effect modifiers of other risk factors. This possibility will be accounted for in the plan of analysis (Section 9.3). However, we assume already that the following factors might play a role:

- Inpatient KMC treatment;
- Episode apnea;
- Hypoglycemia;
- Seizures;
- Post hospitalization illnesses that may have neurological sequelae, including measles, meningitis and malaria;
- Post hospitalization illness that is not associated with specific neurological sequelae, but that could impact growth and development (e.g.: pneumonia, gastro-intestinal and feeding problems, anaemia).
- Feeding: Breast milk or formula.
- Social –economic situation of parents, including educational level of parents
- Use of tobacco, alcohol, or misoprostol during pregnancy;

It is likely that infants that participate in the follow-up during this study will receive a closer medical follow- up than what they would receive without the implementation of the study. As such, it is likely that their health status during the study is better compared to what it would be if they had not participated in the study, as they will be receiving relevant vaccinations and will be followed-up for infections that are endemic in Port-au-Prince. Any associations we therefore find between risk factors (of mothers or morbidities and treatment at CRUO) and negative outcomes (mortality or developmental) will likely underestimate the true burden of these negative outcomes in the general population.

12 Statistical considerations

12.1 Sample size for the cohort

The study will include a cohort of infants of normal weight and LBW infants and aims to document their short term and longer term outcomes (including developmental progress) at 3, 6, ~~and~~ 12, 15, 18, 21 and 24 ~~-~~months of gestational age and after discharge from CRUO. The outcomes of the LBW infants will be compared with the normal weight infants and risk factors for negative outcomes will be identified. Additionally, within the LBW group of infants we will aim to identify particular risk factors for negative outcomes in terms of mortality and neurodevelopment.

The exposures that will be further analysed at these three follow-up points will include (among others): a) actual weight at birth (including sub-groups of LBW); b) treatment provided during hospitalisation; c) gestational age at birth; d) factors associated with the mother (parity, attending ante-natal sessions; e) morbidities presented during hospitalisation etc). The outcomes under scrutiny will include: a) mortality during the follow-up period, b) weight, c) health status, d) scoring on standardised neurodevelopmental scales of the BSID.

As there is very limited published evidence using a similar cohort of infants in a low resource setting, establishing reliable assumptions for the calculation of a sample size is challenging. Moreover, there is no evidence published for this group in the Haitian context either. For the sample size calculations we have therefore had to base our assumptions on data collected

at CRUO during 2013 and published data on mortality in infants born in Nigeria, Kenya and Tanzania [44] [45] [46].

In order to ensure a sufficient sample size to compare LBW with normal weight infants we assume that our 'exposure' is LBW and the 'outcome' is mortality. In Tanzania they identified that the relative risk for mortality in LBW and HIV-negative infants (born to HIV positive mothers) compared to normal weight infants was 3.16 [45]. The neonatal mortality incidence rate in HIV negative infants in Kenya was determined to be six-fold higher in LBW infants compared to normal weight infants [46]. In Haiti it is likely that the mortality in LBW infants will be similar to that seen Kenya and Tanzania. In CRUO during 2013 approximately 47% of infants were LBW and the remainder were normal weight (therefore a ratio of 1:1 for LBW: normal weight). Taking all this information into consideration, we made the following assumptions for the sample size calculation: 1) two-sided significance level of 95%; 2) power of the study is 80%;3) ratio of unexposed/exposed is 1; 4) expected relative risk of 3; 5) expected proportion of outcome in unexposed group is 5%. This generates a sample size calculation in Open Epi of 160 infants in the exposed group and 160 infants in the unexposed group (total 320 infants). Therefore 160 infants of LBW and 160 infants of normal weight would be required.

In order to be able to have a sufficient sample size to identify additional risk factors within the LBW infants discharged from CRUO we assume that the 'exposure' in different categories of LBW (very LBW and extremely LBW, where VLBW= <1000g and ELBW= <1500g) and the outcome is mortality. Unfortunately, we were unable to find any specifically pertinent published evidence. Therefore we used data from a four-year study in a neonatal care facility in Nigeria [44]that documented that the mortality in LBW infants. The study determined that in the unexposed group (LBW only), the mortality was 10.8% (44/406 infants), but that the combined mortality for the exposed group (VBLW and ELBW) was 62.6% (72/115 infants), with the higher proportion of deaths in ELBW infants. As this study was based inside a healthcare facility, we would expect the mortality rate in Haitian infants who are discharged from a healthcare facility to be lower, around 5% (i.e. 5% mortality in the unexposed group for discharged infants). During 2013 in CRUO, 1047 infants were born that were <2.5kg (i.e. 47% out of all infants born). Out of this group of infants, 445 (42.5%) weighed between 1.75-2.5kgs, and 602 (57.5%) weighed <1.75kgs (i.e. 1045 VBLW and ELBW combined). If we consider the first group as LBW and the second group as VLBW and ELBW, then the ratio of non-exposed to exposed would be 0.74 (around 3 non-exposed to 4 exposed).

We used the following assumptions then for the calculation of the sample size: 1) two-sided significance level of 95%; 2) power of the study is 80%; 3) ratio of unexposed/exposed is 0.75; 4) expected relative risk is 3; 5) expected proportion of outcome in unexposed group is 5%. This generates a sample size calculation in Open Epi of 191 infants in the exposed group (VLBW and ELBW infants) and 143 infants in the unexposed group (LBW excluding VLBW and ELBW infants), therefore a total of 334 infants.

Therefore, considering both sample size calculations, the following numbers of infants would need to be included:

- Normal weight infants:160 infants;
- LBW infants (including VLBW and ELBA): 334 infants.

This is a total of 494 infants. Taking into consideration an estimated default rate of 20%, we would need to include 192 normal weight infants and 401 LWB for a total of 593 infants during the entire study period.

12.2 Analysis and Statistical methods

We will conduct a descriptive analysis of all variables in the study including proportions and their respective 95% confidence intervals, means and medians for continuous variables and stratified by categories such as weight class, gender and estimated gestational age.

A crude analysis (using Cox or Poisson regression) will be performed to calculate the relative risk of outcomes to baseline variables and exposures of interest. A multivariable model will then be constructed to calculate the relative risk adjusting for the impact of confounding and effect modification by baseline and exposure variables.

As data are collected at several time points for each infant, the analysis will be adjusted to account for the clustering of measurements within each infant group. An appropriate method of analysis, for example, multi-level modelling, will be evaluated after investigation of the data for loss to follow-up and missing vales and missing data patterns.

13 Reporting

Limitations will be reported in the Discussion section, following this sequence: (1) a brief synopsis of the key findings, (2) consideration of possible mechanisms and explanations, (3) comparison with relevant findings from other published novel studies, and, whenever possible, including a systematic review combining the results of the current study with the results of previous relevant studies, (4) limitations of the present study, and methods used to minimise and compensate for those limitations, (5) a brief section that summarises the clinical and research implications of the work, as appropriate. Imprecision in outcome measurements and diagnosis will be reported. During the description of the results differences between statistical significance and clinical importance will be always clearly stated.

14 Quality control

Assuring the quality of our data collection and compilation will be one of the most priority. This will be managed at field level by the principal investigator, medical coordination and mission epidemiologist and at HQ level by our coordinating epidemiologist and principal investigator.

Data collections tools will be based on what is currently in place in CRUO with some additions, namely neurologic and developmental assessment and specific birth weight categories (these for the infants that are in follow-up component of the study post-discharge). All tools and data produced with them will only be included once it is clear that all persons using them are proficient in their use and in trouble shooting.

To minimise data-entry errors, data will be entered into the Excel based file twice, by two separate operators. Logical checks will be applied regularly. The two datasets will be compared digitally for eventual differences and missing data.

15 Ethical considerations

15.1 Vulnerable population

Any kind of research involving children should be considered ethically problematic and we willingly and openly accept a higher level of scrutiny. The burden is on us to make it clear that these already vulnerable infants will not be exposed to harm. The study aims to look at long term outcomes in infants who receive care in our facility; there is no intervention apart from the standard of care that is offered in our health facility. All infants in the study will receive medical care that is both contextually and medically appropriate for their medical condition.

We acknowledge openly that these infants are neither capable of consent or assent. Consent will be given by the legal guardian and we will ensure that they have a clear understanding of the study, its goals and the implications for the infant (See consent form: Annex 1). As we are extending the study period and asking mothers to provide additional information regarding their pregnancy, we will have to re-consent all the infants/mothers that remain enrolled in the study after 12 months follow up. A new consent form for this purpose has been created (See consent form Annex 1.2)

15.2 Benefit for participants and community

Access to neonatal and paediatric care in Haiti is limited. There are very few paediatricians and even fewer who are trained in neonatology. MSF has chosen to engage in this speciality as we see a gap in the services offered at CRUO if we do not also consider the infants who are the product of the complicated pregnancies we accept.

On a community level, the results of this study could help guide us on future programme direction and where to emphasize our resources. If we can tease out what factors most influence the long term outcome (positive or negative) then we can better inform the choices we make when offering neonatal services within our structures. This information will be shared with local authorities who in turn can direct their programmes to focus resources where the positive impact was highest. Examples of such could be informing on neonatal resuscitation protocols, medical treatment options and increased capacity to give parents a more informed idea on the long term outcomes of their child.

The infants themselves will benefit from a physical examination by a paediatrician and a nurse which will include assessment and treatment for uncomplicated infections not necessitating hospital admission and feeding difficulties. It is acknowledged that the follow-up itself could have a potential impact on the long term outcome (i.e. an infant who is seen in follow-up and treated for a basic ailment is in a better position than an infant who does not receive this follow-up). However, all infants in the study will receive this care, so amongst the cohort the standard of care is the same.

We will also assess the vaccination coverage and catch up as necessary and orient the family to the closest public health structure offering vaccine services. For the caregivers and mothers specifically we will offer continued advice on breastfeeding, family planning and infant care. Further, if developmental issues do surface, we can inform the family and offer them counselling and/or a clearer picture of long term prognosis for the infant. No rehabilitation services are present in Haiti so there are no referral options.

Our mental health team from CRUO will give training to the study doctors and nurses in how to provide this information to the caregivers and how to handle their bereavement. They will help prepare us with written documentation for parents as well as advice on referral.

15.3 Confidentiality

Any and all data collected throughout the study will remain strictly confidential. Data will be kept in a secure and locked place and will only be accessed by approved study personnel when needed for purposes of patient care or study analysis.

The patient's identity will only be known to study staff and all documentation and files will contain only the patient's file number. We will need to keep one register with the ~~patients~~patients' name and contact information so that we can link patients to files, but also to facilitate follow-up and tracking of patients between follow-up appointments. These will be kept electronically in a password protected file (with the password only known to the Medical Coordinator and Principal Investigator) and in paper format in a locked cabinet.

We will assure parents that there is no way that information in the patient files can lead to identification of the participant. This statement is also to be included in the consent form and will be verbally discussed with the legal guardian at when consent is being signed. Data will be entered into databases that are password protected and these will not include the patients or caregivers' names or contact details. All paper versions of patient forms will be kept in secure medical data storage facilities in CRUO for a period of 5 years. Electronic files will be sent to headquarters in Amsterdam following the completion of the study.

15.4 Cooperation with national and local partners

The study has been discussed with the department of maternal and child health at the MSPP. They are aware of and interested in the study. For the time being they do not want to play an active role, but we remain open to this option and also to include them as collaborators and investigators if they have an interest for this and offer them the opportunity to feedback and comment on the protocol.

15.5 Benefits for the programme, community and nationally

As mentioned, having a clearer understanding of the long term outcomes of infants treated in CRUO will on the one hand help MSF guide it's neonatal and paediatric programmes, but can also help to inform other such programmes in low resource settings on where to put the limited financial and human resources they have available, and where to set limits in treatment in order not to do harm.

At country level, MSF/OCA will disseminate the results of the study and advocate for increased focus on the areas where we saw the most positive results. Further we hope that the results will help build the body of literature on this topic and assist others in similar contexts in guiding their programmes in setting limits in treatment in order not to do harm.

Some staff members will benefit from training on development and neurological assessment which can be used in CRUO and in their own practices.

15.6 Reporting

An interim analysis will be conducted following the first 6 months into the study, which will describe the included cohort of babies. Further analysis and reporting will be conducted at

the end of 6, 12 and 18 months assessments. Then a final report will be written at the end of the study with a full analysis of the results. We will submit the final results to a peer reviewed journal (see table: 16 for reporting objectives).

15.7 Incentives and compensation

No financial incentive is anticipated for the duration of the study. However, we recognize that for the patients included in the discharged cohort that it may be difficult for families to travel around Port-au-Prince to come to the follow-up visits. Distances are often far and with poor public transport and terrible traffic this may be a barrier. We will consider, for those within a certain travel distance that we reimburse their travel fees to a pre-determined rate.

All infants in the discharged cohort will receive a physical examination by a paediatrician and a nurse which will include assessment and treatment for uncomplicated infections not necessitating hospital admission and feeding difficulties. Health problems beyond our capacity will be referred to the closest structure in which care is available. We will also assess the vaccination status and catch up as necessary and orient the family to the closest public health structure offering vaccine services. As all infants born will have been born in CRUO, their mothers will have received options for birth control prior to discharge. We would like to use the opportunity of the mothers coming back for their infant's follow-up to monitor any side effects and continue (or change) the method chosen. This can function as a form of incentive, but also as public health benefit to keep these at risk mothers on longer term birth control. Currently, mothers do sporadically return to CRUO for follow-up of their birth control method.

15.8 Potential risks

We see very few potential risks of this study. There is no intervention; rather we are examining the outcomes of the infants who receive medical care in our facility. All infants are offered the same level of care based on their medical needs.

We will be offering basic medical care to those infants who require it. There may be side effects from the treatments we offer, such as allergic reactions to antibiotics. This is no different to the risks posed if they had consulted a paediatrician for the problems outside of the study.

We are offering neurological and development screening, which in itself poses no risk. However, the impact for the family of receiving news that their infant is (or potentially is) physically and neurologically delayed or impaired could be very distressing for the family. We will be forcing a reality on family members that they may not be prepared for, that might be hard or that they are not willing to accept. This news could have an impact on the care they give to their infant. Further, we are well aware that referral options are extremely limited in Haiti. In 2013 we achieved only one successful surgical transfer. Even after extensive searching, we remain unaware of any public medical structures that have the capacity to manage either paediatric surgery or follow up of neurodevelopmental delays. The few private structures that do exist tend to be chronically full and work with outside funding which often leads to ruptures of services.

Our CRUO mental health team will be involved from the start of the study with training for the study staff on delivering bad news as well as bereavement counselling should it be necessary. They will help us develop written and pictorial information flyers for the families.

16 Organigram and responsibilities

The study will be conducted and funded by MSF-OCA (see Table 4 for breakdown of the study team).

Table 4 - Co-investigators involved in the trial

Institute	Responsibility	Person	Position:
MSF/OCA- Haiti	• Coordination of study at field level • Supervision of Study staff, inputting of data into tools, training and follow-up of staff. • Quality control of daily data encoding.	Dr. Marjorie Hillaire	Haitian principal investigator
MSF-/OCA	• Drafting of initial study protocol • Input and re-writing of any study amendments • Recruitment of Study staff; • Ordering of all necessary equipment; • Ensuring submission of protocols and amendments for ERB approval from MSF and Haiti; • Preparation of data collections tools and forms and adaptation as needed. • Follow up of data entry quality and analysis • Daily monitoring and quality control of data • Data analysis and support for report writing • Direct support to national primary investigator as needed.	Lindsay Bryson	Principal Investigator (2013-XXX) (Medical Coordinator 2012-2015)
MSF/OCA- Haiti	• Drafting of initial study protocol	Dr. Liam Reilly Dr. Elizabeth Ledger	Expat Pediatricians-CRUO 2013/2014
MSF-OCA-Haiti	• Daily follow up of study to assure with national PI the proper functioning of the study. • Assurance of all appropriate ERB approvals in Haiti and with MSF • Supervision and support to study team. • Follow up of materials needed • Follow up of training needs.	Marine Berthet	Medical coordinator OCA-Haiti mission (June 2015-May 2017)
MSF-OCA-Haiti	• Daily data monitoring and quality control • Support to study staff with all data tools • Data Analysis and report writing	Olu Faniyan	Epidemiologist, MSF-OCA Haiti (July 2015—June 2016)
MSF-OCA Amsterdam	• Drafting of initial study Protocol • General coordination of study, • validation of protocol and tools • Reporting and Validation • Data Analysis and report writing	Annick Lenglet	Epidemiologist/MSF OCA
MSF/OCA-Amsterdam	• Drafting of initial study protocol • Technical Pediatric guidance	Harriet Roggeveen	OCA Pediatrics advisor.
Independent consultant, MSF Manson Unit, London	• Technical support to statistical aspects of the study design, support in data analysis and manuscript drafting.	Cono Ariti	Statistician

17 Time frame

Period	Objective	Result
October 2013-May 2014	Writing protocol	Complete
June/July 2014	MSF ERB review and (+) feedback	Complete
July/August 2014	Haiti Ethics review and (+) feedback	Complete
Early Oct 2014	Start of inclusion (estimate of 100 infants per month)	Complete
Feb-15	End of inclusion	Complete
December 2014 to May 2017	Follow-up visits will continue throughout 2015/2016. With the extension to 24 months follow up, final follow up assessments will likely be completed in May 2017.	In progress
Oct-Nov 2015	Completion of first 6 months analysis of inclusion cohort. Report will be submitted to both MSF and Haitian ERB as a progress report.	Complete
May-June 2016	Completion of first 12 months analysis of inclusion cohort. Report will be submitted to both MSF and Haitian ERB as a progress report.	Pending completion of 12 months assessments
Oct-Nov 2016	Completion of first 18 months analysis of inclusion cohort. Report will be submitted to both MSF and Haitian ERB as a progress report.	Pending completion of 18 months assessments
May-July 2017	Completion of first 24 months analysis of inclusion cohort. Report will be submitted to both MSF and Haitian ERB and to peer review journal.	Pending completion of 24 months assessments

Period	Objective	Result
~~October 2013-May 2014~~	~~Writing protocol~~	~~Complete~~
~~June/July 2014~~	~~MSF ERB review and (+) feedback~~	~~Complete~~
~~July/August 2014~~	~~Haiti Ethics review and (+) feedback~~	~~Complete~~
~~Early Oct 2014~~	~~Start of inclusion (estimate of 100 infants per month)~~	~~Complete~~
~~February 2015~~	~~End of inclusion~~	~~Complete~~

December 2014 to November 2016	Follow-up visits will continue throughout 2015/2016. With the extension to 18 months follow up, final follow up assessments will likely be completed in November 2016.	In progress
April-June 2015	Completion of analysis of inclusion cohort. Report will be submitted to both MSF and Haitian ERB as a progress report.	Complete
December 2015-January 2016	Completion of analysis of 6 months assessments. Report will be submitted to both MSF and Haitian ERB as a progress report.	Pending completion of 6 months assessments
June-July 2016	Completion of analysis of 12 months assessments. Report will be submitted to both MSF and Haitian ERB as a progress report.	Pending completion of 12 months assessments
January-April 2017	Completion of 18 months assessment and study closure. Complete analysis of all collected study data and writing of final reports with submission to MSF/Haiti ERBs and to peer review journal.	Pending completion of 18 months assessments

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20 Annexes

1. Consent form
2. Inclusion form
3. Discharge from hospitalization form
4. Routine neo inpatient data
5. Surveillance form
6. 3, 6, 12 month follow-up form
7. Bayley scale
8. CRUO resuscitation guidelines
9. Timeframe