Bronchopulmonary dysplasia and perinatal glucocorticoids in preterm infants: changing practice based on evidence
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Citation for published version (APA):

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Chapter 7

Study protocol: Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants (the SToP-BPD study); a multicenter randomised placebo controlled trial

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Submitted to BMC Pediatrics
Abstract

Background: Randomised controlled trials have shown that treatment of chronically ventilated preterm infants after the first week of life with dexamethasone reduces the incidence of the combined outcome death or bronchopulmonary dysplasia (BPD). However, there are concerns that its use may increase the risk of adverse neurodevelopmental outcome. Hydrocortisone has been suggested as an alternative therapy. So far no randomised controlled trial has investigated its efficacy when administered after the first week of life to ventilated preterm infants.

Methods/Design: The proposed trial is a randomised double blind placebo controlled multicenter study in very low birth weight infants (gestational age <30 weeks and/or birth weight <1250 grams), who are ventilator dependent at a postnatal age of 7 – 14 days and are suspected with a diagnosis of developing BPD. Hydrocortisone (cumulative dose 72.5 mg/kg) or placebo will be administered during a 22 day tapering schedule. Primary outcome measure is survival free of BPD at 36 weeks postmenstrual age. Secondary outcomes are short term effects on the pulmonary condition, adverse effects during hospitalization, and long-term neurodevelopmental sequelae assessed at 2 years corrected gestational age. We expect an inclusion of 400 patients (200 per group) to be feasible in an inclusion period of three years. An absolute risk reduction for the outcome death or BPD of 15% or more (number needed to treat=7) is considered clinically relevant. With an estimated a priori risk for death or BPD at 36 weeks postmenstrual age in preterm infants less than 30 weeks gestation and ventilated in the second week of life of 60%, a type I error of 5% (2 tailed) this trial has a power of 80% to detect an absolute risk reduction of 15% for this outcome in the treated group. Analysis will be by intention to treat.

Discussion: This trial will determine the role of postnatal hydrocortisone administration at a moderately early onset for the reduction of the combined outcome death or BPD in ventilator dependent preterm infants and its possible adverse effects.

Trial registration number: Clinical trials, protocol registration system: registered in DTR nr 2010/x; AMC MEC 10/297
Background

Bronchopulmonary dysplasia (BPD) is the most common complication of premature birth, with a reported incidence of 8% to 35%.[1,2] BPD is characterized by chronic respiratory distress, the need for prolonged respiratory support, an increased risk of recurrent pulmonary infections, airway hyperreactivity during the first years of life,[3] and life-long alterations in lung function.[4-6] Patients with established BPD have high rates of readmissions and utilization of health services resulting in tremendous societal costs compared to children without BPD.[7-9] Furthermore, BPD is considered an important risk factor for adverse neurodevelopmental outcome after premature birth.[10-14]

In addition to direct mechanical injury, caused by artificial ventilation and oxygen toxicity, pulmonary inflammation has been identified as an important mediator in the development of BPD.[15-17] This is the rationale for treating these patients with glucocorticoids, a well known anti-inflammatory agent. Randomised controlled trials (RCTs) summarized in several systematic reviews have shown that postnatal systemic glucocorticoids, mainly dexamethasone, reduce the risk of the combined outcome death or BPD in ventilated preterm infants.[18,19] Furthermore, systemic glucocorticoids seem to be most effective when administered in a time frame of 7 to 14 days postnatal age, the so-called moderately early treatment onset.[20,21] However, initiating dexamethasone treatment in the first days of life seems to be associated with an increased risk of cerebral palsy (CP). Although this complication has not been reported by RCTs investigating dexamethasone treatment initiated after the first week of life, these alarming reports have resulted in a general concern on the use of dexamethasone in preterm infants.[22-24] Based on this concern, the American Academy of Pediatrics, Canadian Paediatric Society, and the European Association of Perinatal Medicine have stated that clinical trials should be performed to investigate the use of alternative anti-inflammatory glucocorticoids, such as the less potent glucocorticoid hydrocortisone.[25,26]

Animal data suggest that hydrocortisone has a less detrimental effect on the brain than dexamethasone.[27] No placebo controlled RCT has investigated the use of hydrocortisone after the first week in life in ventilator dependent preterm infants.[28] Eight RCTs including 880 infants investigated a low hydrocortisone dose started within < 72 hours after birth (early treatment). Meta-analysis of these trials failed to show a clear reduction in the incidence of BPD or harmful effects.[29] Only one of these trials reported long-term follow-up, showing no differences in adverse neurodevelopmental sequelae.[30] These findings are supported by several historical cohort studies, showing no increased risk of adverse neurodevelopmental outcome in hydrocortisone treated infants.[31-33]
In most NICUs preterm infants who are ventilator-dependent in the second week of life are no longer treated with glucocorticoids.\cite{34,35} Infants are kept on the ventilator allowing spontaneous recovery of lung function over time, sometimes supported by other interventions, such as diuretics and inhalation therapy. With this approach, some infants can be successfully weaned and extubated. Only those infants that remain ventilator dependent after 3-4 weeks are treated with glucocorticoids, with the primary objective to wean and extubate.

Although this approach will undoubtedly result in successful extubation of most infants with the lowest possible use of glucocorticoids, the question remains if this is also the best strategy in reducing the incidence of BPD in preterm infants ventilated after 7 days of life.\cite{36,37}

This question seems justified and relevant because BPD, and not failure to extubate, is associated with adverse medium- and long-term outcome. This is the main reason why the primary outcome of this study is death or BPD and not failure to extubate. Studies using dexamethasone have shown that glucocorticoids significantly reduce the incidence of death or BPD at 36 weeks PMA and that treatment is most effective when started in the second week of life.

Despite the ongoing concerns on their use, systemic glucocorticoids are still used in approximately 10% of the preterm infants at risk for BPD.\cite{34,35,37} Dexamethasone is still the most widely used glucocorticoid drug, but its dose has been significantly reduced and administration is often postponed until the 3rd or 4th week of life.\cite{22} As an alternative, many clinicians have started to use hydrocortisone, despite the fact that its efficacy in preterm infants remains to be proven.

The NICU at the University Medical Center Utrecht has historically used hydrocortisone for chronically ventilated preterm infants. Retrospective studies seem to indicate that hydrocortisone is effective in reducing BPD, without causing serious adverse effects. However, these findings need to be confirmed or refuted by a large randomized placebo controlled trial. Despite the absence of randomized evidence, four out of the 10 Dutch NICUs switched from dexamethasone to hydrocortisone. This diversity in treatment between NICUs is undesirable and as a first step to resolve this diversity in treatment, all 10 Dutch NICUs have indicated that a RCT comparing hydrocortisone with placebo is urgently needed. Since the NICUs which already use hydrocortisone are reluctant or refuse to prescribe dexamethasone as trial medication, a RCT comparing dexamethasone versus hydrocortisone is not possible.
Methods/Design

Study aims, design and setting
This will be a multicenter double-blind placebo-controlled randomized study to investigate if hydrocortisone is safe and effective in reducing the incidence of the combined outcome death or BPD at 36 weeks PMA in chronically ventilated preterm infants, as compared to placebo. This study does not aim to successfully extubate ventilator-dependent preterm infants with the lowest possible use of glucocorticoids (i.e. hydrocortisone), but to use glucocorticoids as an early intervention (7-14 d after birth) to reduce the risk of death or BPD in these ventilator-dependent preterm infants. From this point of view the treatment strategy is fundamentally different from what is currently used in daily clinical practice.

All 10 NICUs in the Netherlands and 5 NICUs in Belgium will be recruiting patients into the SToP-BPD trial.

Inclusion criteria
Preterm infants with a gestational age < 30 weeks and/or birth weight < 1250 grams with evolving BPD, defined as being ventilator dependent at 7-14 days PNA with a respiratory index (MAwP x FiO\textsubscript{2}) of ≥ 3.5. This index should be present for more than 12 hours per day for at least 48 hours and must ensure normal oxygen saturation (86-94%) and pCO\textsubscript{2} values in premature infants (5.0-7.0 kPa).

Exclusion criteria
Infants with chromosomal defects (e.g. trisomy 13, 18, 21) or major congenital malformations that are expected to compromise lung function (e.g. surfactant protein deficiencies, congenital diaphragmatic hernia) or result in chronic ventilation (e.g. Pierre Robin sequence), or increase the risk of death or adverse neurodevelopmental outcome (congenital cerebral malformations) will be excluded.

Although (suspected or proven) sepsis, pneumonia, necrotizing enterocolitis (NEC) and patent ductus arteriosus (PDA) are well-known causes of respiratory failure, these diagnoses are know to be independent risk factors for developing BPD. Therefore, these diagnoses are not considered to be exclusion criteria. The following should be taken into consideration:

In ventilator-dependent cases of sepsis and pneumonia the attending physician may start antibiotics and await the effect on respiratory drive/ pulmonary status for 48 hours. If the patient meets the inclusion criteria after 48 hour, he/she is eligible for inclusion.

It is strongly recommended to screen all ventilator-dependent preterm infants for a PDA at 5 days PNA. In case of a hemodynamic important PDA, medical intervention
according to local protocols should be started as soon as possible. Ibuprofen or indomethacin treatment should not be combined with glucocorticoids, because it has been suggested that this combination will increase the risk of intestinal perforation. If, subsequently, the patient can’t be extubated following medical treatment or requires surgical PDA closure, he/she should be included in the study - provided that all inclusion criteria are met.
If the physician considers extubation not an option because of the general condition of the infant (e.g. NEC with severe hemodynamic instability and severe abdominal distension) inclusion in the study can be postponed until the maximum of 14 days PNA.

Consent
Informed written consent will be obtained from the parents or care-givers after a full verbal and written explanation prior to randomisation for the study. The attending paediatrician will meet with parents during the intervention period to ensure that they understand the study procedures and continue with their consent to participate in the study. The right of a parent or patient to refuse participation without giving reasons will be respected. The parents will remain free to withdraw their child at any time from the study without consequences for further treatment. Approval for the study has been obtained from the Amsterdam Medical Research Ethics Committee and the Local Research Ethics Committee of each participating hospital.

Randomisation
In case of ventilator dependency after day 7 of life with a suspected diagnosis of developing BPD, parents receive the study information as soon as possible allowing them sufficient time to consider participation. The actual decision to include the patient in the trial should be made between day 7 and 14 PNA. The first dose of study medication should be administered within 24 hours after randomization. Randomization will be centrally controlled and web-based using a computer program designed for this study. This trial will be protected from selection bias by using concealed, stratified and blocked randomisation. Randomisation will be stratified per center and according to gestational age stratum (Stratum A: 24-26 weeks; Stratum B: 26-28 weeks; Stratum C: >28 weeks), in order to achieve an equal distribution in both treatment arms. The allocation ratio will be 1:1 with block randomisation using variable block sizes. Multiple birth infants will be randomised independently, unless the parents or caretakers explicitly demand that the siblings should be treated according to the same treatment arm. An automated mechanism to perform twin randomisation is in place. The infants’ parents and all
members of the medical team, including investigators, remain blinded to group assignment throughout the study.

Clinical management
All randomized patients will be treated according to the guidelines of the individual NICUs. All participating NICUs explore treatable causes of ventilator dependency during the first week of life, such as patent ductus arteriosus, sepsis and pneumonia as much as possible and to treat these according to the department protocol. Although all of these conditions can be an alternative cause of respiratory failure, they are known risk factors for developing BPD and therefore are not considered exclusion criteria. This trial will monitor the important co-interventions and conditions.

Preparation of the trial medication
The local pharmacy is in charge of preparing the hydrocortisone and placebo and will distribute the medication in unlabelled syringes of 2 ml, tagged with the patients’ trial identification number of the hospital and its name. The infants of the hydrocortisone group receive hemisuccinate hydrocortisone 5mg/kg/day Q.I.D for 7 days, followed by 3.75 mg/kg/day T.I.D. for 5 days, subsequently lowering the frequency by one dose every 5 day. This leads to a total duration of therapy of 22 days and a cumulative dose of 72.5 mg/kg hydrocortisone. The infants in the control group receive saline placebo for the entire 22-day period in the same frequency as the hydrocortisone group. Both saline and hydrocortisone schedules will be calculated according to weight on the day of randomisation and not adjusted to the actual weight during the tapering schedule. The preferred route of administration will be intravenous. However, if the participating infant lacks intravenous access the study medication will be administrated enterally.

Discontinuing study medication
In case of life threatening deterioration of the pulmonary condition, indicated by a respiratory index (MAwP x FiO$_2$) $>$10 for more than 6 consecutive hours, the attending physician may decide to start open label hydrocortisone therapy in an attempt to improve the pulmonary condition. A second possible scenario for discontinuing the study medication will be in case if the pulmonary condition of the patient is stable (RI $<$ 10) but not improving over time. In these circumstances open label hydrocortisone may be considered if the following conditions are met: extubation was attempted (extubation trial) within 24 hours before considering open label treatment and this attempt failed. The patient is on study medication for at least 10 days.
The open label therapy dosage schedule is similar to that used in the study. At that point in time the study medication is stopped and the patient will be recorded as “treatment failure”. In case of treatment failure the following data will be collected: timing of treatment failure, ventilator support and settings, type of open label medication, starting date, cumulative dose and duration of rescue therapy. The patients will be followed as all other patients until the clinical endpoints occur or until end of follow up.

**Open label glucocorticoids after study medication protocol**

Patients still on mechanical ventilation after completion of the study medication, i.e. day 22, may be treated with open label hydrocortisone. In such cases the physician should first attempt extubation before considering open label use. Considering the fact that this study investigates the efficacy of hydrocortisone, using a treatment regimen similar to the study is highly recommended. Data on the starting date, cumulative dose and duration of rescue therapy are collected.

**Outcomes**

*Primary outcome*

The primary outcome will be the dichotomous variable *BPD free survival at 36 weeks PMA*. BPD at 36 weeks PMA will be assessed according to the NIHCHD Consensus Statement defining normal oxygen saturation as 86%-94%. The severity of the BPD will be assessed as proposed by Jobe et.al., since the severity of BPD has a high association with neurodevelopmental sequelae. In case of supplemental oxygen delivery >21% and < 30% or low flow at 36 weeks PMA, the oxygen reduction test as described by Walsh et.al., should be performed. A positive oxygen reduction test has a high correlation with the risk on discharge home with oxygen, the length of hospital stay, and pulmonary morbidity requiring hospital readmission during the first year of life.

*Secondary endpoints*

Short term outcomes (before discharge from hospital):
- treatment failure by discontinuing study medication as previously described
- mortality at 28 days PNA, 36 weeks PMA and at hospital discharge
- BPD at 28 days
- failure to extubate 3, 7, 14 and 21 days after initiating therapy
- duration of mechanical ventilation
- use of “rescue treatment” with hydrocortisone outside the study protocol
- total time on supplemental oxygen
- length of hospital stay
• incidence of hypertension, defined as systolic blood pressure > 2SD of standardized values used in the department
• hyperglycemia requiring the use of insulin therapy
• nosocomial infection, like sepsis, meningitis and pneumonia
• hemodynamic significant patent ductus arteriosus for which medical intervention or surgical ligation is needed
• necrotising enterocolitis (NEC), diagnosed at surgery, autopsy or by radiographic finding of pneumotosis intestinalis or hepatobiliary gas (Bell stage II)
• gastrointestinal bleeding
• isolated gastrointestinal perforation diagnosed on abdominal radiography
• intraventricular haemorrhage (IVH) and/or periventricular leucomalacia (PVL), including grading on cerebral ultrasonography according to protocol defined by Ment et.al.\[40\]
• retinopathy of prematurity, including grading following international classification\[41\]
• weight gain, head circumference and length gain at 36 weeks PMA

*Long-term health and neurodevelopmental sequelae (assessed at 2 years CGA)*
• mortality
• readmissions since first discharge home
• weight, length and head circumference at 24 months c.a.
• Bayley Scales of Infant Development III, Mental Developmental Index and Psychomotor Developmental Index
• cerebral palsy and severity of cerebral palsy using gross motor function classification system
• hearing loss requiring hearing aids
• blindness
• behavioural problems (child behavior checklist)

**Data collection**
Baseline characteristics are collected prior to inclusion and randomization with respect to the following baseline characteristics: demographic details and patient characteristics, such as gestational age, small for gestational age, antenatal problems, antenatal steroids, surfactant therapy, mode of delivery, resuscitation details, Apgar scores, presence of IVH/PVL, and occurrence of PDA. Base line characteristics on ventilator settings, gas exchange will be collected on day of randomization.
Timing, dose and duration of all co-interventions, such as methylxanthines, diuretics, bronchodilators/inhalation corticosteroids and inhaled nitric oxide, as well as the ventilation mode with the ventilator settings will be recorded and analyzed.
Statistical analysis

Normally distributed data will be presented as mean ± standard deviations, not-normally distributed data as medians and (interquartile) ranges. Categorical data will be analysed using the Chi-square test. Continuous data will be analysed using the Student’s t test or Mann-Whitney test as appropriate. Both intention-to-treat and per-protocol analysis will be employed since use of open label glucocorticoids modulates the found risk differences. The effect of hydrocortisone on the primary outcome death or BPD will be assessed by multi-variable logistic regression analysis including possible confounders. Statistical significance is set at p < 0.05.

Interim analyses

An external and independent Data Monitoring Committee (DMC) will conduct reviews of patient safety presented initially on hydrocortisone versus placebo basis. Data summaries for the DMC will be prepared by a statistician who is not a member of the investigating team. Formal interim analyses will be conducted when approximately 25%, 50% and 75% of the anticipated outcome data are available. The DMC will have access to all safety data and will be in a position to make recommendations to the trial's Steering Committee - should a risk to the safety of participants arise. This safety data will include, but not be restricted to, serious adverse events and the safety outcomes listed as secondary outcomes. The results of the interim analyses will remain confidential – only the unblinded statistician will have access to the unblinded analyses. If the DMC recommends modification or cessation of the study protocol, this will be discussed with the Steering Committee, who will make the decision. The DMC will be composed of 3 individuals with expertise and extensive experience in newborn ventilation, trial management or statistics. The Steering Committee will propose a detailed mandate and review this with the DMC, from the outset. None of the members will be from institutions represented in the study. The DMC will report to the Steering Committee with whom the onus of early closure will ultimately reside. Both the DMC and the Steering Committee will be informed on the implications of recent information on premature stopping of trials.

The investigator will inform the subjects and the reviewing accredited ethics committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited ethics committee, except insofar as suspension would jeopardise the subjects’ health. The investigator will take care that all subjects are kept informed.
Reporting serious adverse events (SAE)

All SAEs will be reported to the principle investigator and the study coordinator via the study website and to the accredited local ethics committee that approved the protocol, according to the requirements of that committee. Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational drug. All adverse events reported spontaneously by the subject’s parents or caregivers or observed by the investigator or his staff will be recorded.

Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered. Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product. The Steering Committee will report expedited the following SUSARs to the local ethics committee:
- SUSARs that have arisen in the clinical trial that was assessed by the ethics committee;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the ethics committee.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the ethics committee. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The Steering Committee will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the Steering Committee has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

Annual safety report

In addition to the expedited reporting of SUSARs, the Trial Steering Committee will submit, once a year throughout the clinical trial, a safety report to the accredited ethics committee, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States.
This safety report consists of:
- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

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

Sample size
The primary outcome parameter is BPD free survival at 36 weeks PMA. The a priori risk of death or BPD in preterm infants less than 30 weeks gestation and ventilated in the second week of life is estimated at 60 – 70%. The meta-analysis on moderately early dexamethasone treatment estimated an absolute risk reduction (ARR) of 25% (NNT=4) compared with placebo. However, there are no data currently available on the efficacy of hydrocortisone and the suggested cumulative dose in the present study is considerably lower compared to previously used dexamethasone doses. Since the shown efficacy of dexamethasone is dependent on the used doses in these trials, we would propose a more conservative approach, defining an ARR of 15% or more (NNT=7) as clinically relevant. With an estimated a priori risk for death or BPD at 36 weeks PMA of 60%, a type I error of 5% (2 tailed) and a power of 80% the number of patients to be included in each treatment arm would be 175 (total 350). Anticipating a 10% drop out of randomized patients, 200 patients need to be included in each treatment arm (total 400). Based on a retrospective analysis of ventilated preterm infants at day 7 of life in the majority of Dutch NICUs we expect a total of 200 eligible patients each year. With an estimated inclusion rate of 66% of eligible patients and an inclusion period of 3 years, a total of 400 patients should be included in the study. For sample size calculation we used Nquery (Statistical Solutions Ltd., Cork, Ireland).
Parents or caregivers can leave the study at any time for any reason if they wish to do so without any consequences. The investigator/attending physician can decide to withdraw a subject from the study in case of prespecified treatment failure.

**Discussion**

This trial will commence recruitment end 2010 and is expected to be completed by December of 2013.

**Organisation**

*Trial Steering Committee*

The Trial Steering Committee (TSC) is the main policy and decision making committee of the study and has final responsibility for the scientific conduct of the study. It will be composed of representatives of the sponsors, of the investigators of the participating centres and of the MCRN. The specific tasks of the TSC are:

- Approve the study protocol
- Approve necessary changes in the protocol based on considerations of feasibility
- Act upon recommendations of the Data Monitoring Committee
- Review performance reports of the study sites
- Resolve operational problems brought before it by the project manager
- Approve study reports and papers for publication.

*Data Monitoring Committee*

An independent Data Monitoring Committee (DMC) will be created specifically for this trial. The DMC will act in advisory capacity to the Steering Committee. Membership of the DMC is:

1. A neonatologist with extensive knowledge of BPD
2. A statistician, with experience with trials and with previous DMCs
3. A pharmacologist, extensive knowledge of the use of hydrocortisone in neonates

*Clinical Project Manager / Central Study Coordinator*

An experienced clinical project manager (CPM) from MCRN will manage the quality of the study according to the Good Clinical Practice (GCP)-guidelines, supervise the data monitoring process, and verify the quality of conduct of all study personnel. The CPM and/or clinical research associate (CRA) will arrange that the study personnel is adequately trained in GCP and study protocol, where needed. The CPM meets regularly with the CRA, data managers, the Data Safety Monitoring Committee (DSMC), financial departments of study centers, and all other relevant parties to assure study progress, quality and financials are according to planning.
The CPM will coordinate regulatory authority and ethics committee submissions. The CPM provides regularly an overall study status report to the Steering Committee.

**Study Monitoring**

The study will be monitored by an experienced monitor from MCRN throughout its duration by means of personal visits to the Investigator’s facilities and through other communications (e.g., telephone calls, written correspondence). Monitoring visits will be scheduled at mutually agreeable times periodically throughout the study and at frequency deemed appropriate for the study. These visits will be conducted to evaluate the progress of the study, ensure the rights and wellbeing of the subjects are protected, check that the reported clinical study data are accurate, complete and verifiable from source documents, and the conduct of the study is in compliance with the approved protocol and amendments, GCP and applicable national regulatory requirements. A monitoring visit will include a review of the essential clinical study documents (regulatory documents, CRFs, source documents, drug disposition records, subject informed consent forms) as well as discussion on the conduct of the study with the Investigator and staff. The Investigator and staff should be available during these visits to facilitate the review of the clinical study records and resolve/document any discrepancies found during the visit.

**Acknowledgements**

This trial is funded by a Project Grant from the ZonMW Priority Medicines for Children nr 11-32010-02.
References


