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Protocolized versus non-protocolized weaning to reduce the duration of invasive mechanical weaning in neonates: a systematic review of all types of studies.

Bas Bol, RN MANP1*, Henriette van Zanten RN PhD2*, Joke Wielenga RN PhD3, Agnes vd Hoogen RN PhD4, Petri Mansvelt RN MANP5, Bronagh Blackwood RN PhD6, Onno Helder RN PhD1.

* Bas Bol and Henriette van Zanten contributed equally at this manuscript.

Corresponding author: Bas Bol, s.bol@erasusmc.nl. Erasmus MC - Sophia Children’s Hospital, Rotterdam, The Netherlands. Wytemaweg 80, postal code 3015CM. Tel: +31107036838.

1Department of Pediatrics, Division of Neonatology, Erasmus Medical Center Rotterdam – Sophia Children’s Hospital, Rotterdam, The Netherlands. 2Neonatal Intensive Care Unit, Leiden University Medical Center, Leiden, The Netherlands. 3Intensive Care Neonatology, Amsterdam University Medical Centers, location Academic Medical Centre, Amsterdam, The Netherlands. 4Department of Neonatology, Wilhelmina Children’s Hospital, University Medical Center, Utrecht, The Netherlands. 5Department of Neonatology, Amalia Children’s Hospital, Radboud University Medical Center, Nijmegen, The Netherlands. 6Center for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen’s University Belfast, Belfast, United Kingdom.

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Erasmus MC, Erasmus University Rotterdam, The Netherlands.

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Abstract:
Mechanical ventilation is one of the most used treatments in neonatology. Prolonged mechanical ventilation is associated with deleterious outcomes. To reduce the ventilation duration, weaning protocols have been developed to achieve extubation in adult and pediatric care in a safe and uniform manner.
We performed a systematic review to obtain all available evidence on the effect of protocolized versus non-protocolized weaning on the duration of invasive mechanical ventilation in critically ill neonates.
The Cochrane Central Register of Controlled Trials; MEDLINE; EMBASE; CINAHL were searched; Web of Science; and the International Clinical Trial Registry Platform, until January 2018. Quantitative and qualitative studies involving neonates which investigated or described protocolized versus non-protocolized weaning were included. Primary outcome was the difference in weaning duration.
A total of 2099 potentially relevant articles were retrieved. Three studies met the inclusion criteria. Of two of these the separate neonatal data could not be obtained. Only one retrospective study was included for this review. This reported a decrease in the mean weaning time from 18 to 5 and 6 days respectively.
Conclusion: There is no robust evidence in the literature to support or disprove the use of a weaning protocol in critically ill neonates.

Keywords: Infant, newborn. Intensive care units, neonatal. Neonatology. Ventilator weaning

Abbreviations:
CI – confidence interval
HRQoL – health related quality of life
ICU – intensive care unit
LOS – length of stay
MV – mechanical ventilation
NICU – neonatal intensive care unit
NS - not significant
PICU – pediatric intensive care unit
RCT – randomized controlled trial
Invasive mechanical ventilation is one of the most used treatments in neonatology. The evidence for protocolized weaning off mechanical ventilation is very limited.
Introduction:

Mechanical ventilation (MV) is one of the most used treatments in neonatology. Both, invasive and non-invasive techniques are extensively used for respiratory support in term and preterm born neonates (1). In recent years there has been growing awareness that invasive ventilation has deleterious effects, such as bronchopulmonary dysplasia and developmental problems, and should be applied/ administered as short as possible (2, 3). To prevent these effects, neonates are weaned off the ventilator and extubated as soon as possible, although 30-40% will require a reintubation (3). Extubation failure is associated with increased risk of morbidity and mortality (4), therefore it is important to attempt extubation at the time when successful extubation is likely. Weaning protocols are still little used but could be useful to achieve extubation in a safe, uniform and less variable way. Decisions on weaning from MV seem to be influenced by many factors, such as nursing involvement, adherence to a protocol or patient to healthcare provider ratio (4-6). There is strong evidence for the benefit of a weaning protocol in adults and up to 70% adult intensive care unit have implemented these (7). Both, in the adult and in the pediatric intensive care unit (PICU) the evidence favours protocolized weaning over non-protocolized weaning, although the evidence in the PICU is less compelling (8, 9).

Weaning protocols are also used in neonatal intensive care (NICU), although less intensively. A study on peri-extubation practices in extremely preterm infants showed that only 36% of the responding units used a guideline or written protocol (4). A Canadian survey confirmed this; 38% of the tertiary NICUs had a protocol to guide the use of MV (10). The evidence for using these protocols in the NICU is scarce. Wielenga et al. in 2016 published a Cochrane review on protocolized versus non-protocolized weaning for invasively ventilated neonates (11). Randomized controlled trials (RCT) on this subject were not found, and conclusions could not be drawn. Therefore the aim of this study was to evaluate and conduct a systematic review of all available evidence for protocolized weaning versus non-protocolized weaning during invasive MV in neonates.
Method:
The method and search strategy was registered in Prospero (ID. CRD42016032412).

Population and setting
Both, quantitative and qualitative studies investigating protocolized weaning compared to non-protocolized weaning practices, and which involved neonates, were included. Neonates were defined as a child under 28 completed days after the expected date of birth (WHO definition)(12). The corresponding authors of studies including both neonates and infants were asked to provide separate data for analysis in this review. If data separation was not possible, these studies were included only if the neonatal sample made up more than 75% of the population sample. Studies were included in which neonates exclusively were mechanically ventilated by endotracheal tube; therefore studies in which infants received ventilation by non-invasive techniques or tracheostomy were excluded. Extubation readiness assessment as a single intervention (e.g. Spontaneous Breathing Trial) was not considered as a weaning protocol.

Intervention and comparator
For this review, protocolized weaning was defined as having used any kind of protocol, with the intention to discontinue invasive mechanical ventilation. Non-protocolized weaning was defined as usual care, e.g. standard practice that incorporated any non-protocolized practice. All sorts of interventions and comparators were included; e.g. a protocol versus standard care. All kinds of professionals were involved, a comparison between a protocol led by the nursing team versus standard care by the registrars or a computerized protocol versus standard care.

Outcomes
In accordance with the ventilation core outcome set developed by Ringrow and colleagues (13), we extracted data on: mortality, health related quality of life (HRQoL), duration of mechanical ventilation, re-intubation, length of stay (LOS), and successful extubation.

Types of study
Both quantitative and qualitative studies were included. The quantitative studies could be (semi-)randomized controlled trials, non-randomized, or cohort studies. Qualitative studies could be case reports or interviews.
Search strategy

This systematic review followed the guidelines outlined in the preferred reporting items for systematic literature reviews and meta-analysis (PRISMA) statement (14). The study protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD, No. 42016032412). The review team, including a librarian of the Erasmus University Medical Center, devised and executed the search strategy. The following databases were searched: the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, Web of Science and the International Clinical Trial Registry Platform. The specific search strategy for each database is presented (table 1). Key words such as protocol, weaning, mechanical ventilation, extubation and neonates were used in the search strategy. Furthermore the reference lists of the identified articles were hand-searched for additional references. Ongoing studies were identified by searching the major clinical trials registries. There was no language restriction.

All databases were searched from start of the digital databank until January 2018.

Study selection

The review team consisted of six researchers (BB, JW, AvdH, HvZ, PM, OH), divided into three pairs. These pairs independently scanned the titles and abstracts of citations identified by the electronic search. Records not meeting the eligibility requirements were excluded. Full-text copies of all potentially relevant studies were obtained. In case of disagreements, consensus was strived for through discussion or consultation of a third researcher. Details of the excluded studies are noted in table 2.

Data extraction

Of eligible articles, the study design, setting, patient characteristics, (co-)interventions, outcome measurements, conclusions, comments, and quality assessments were documented. A data extraction form was used to collect: author, year, design, sample, time points, length of measurement, target range and key results. The extracted data were sent to the corresponding author of the study concerned to verify if the data were abstracted correctly. If necessary, the corresponding author was asked to provide missing data.

Quality assessment and grading

We graded the quality of the selected studies using the QualSyst tool for quantitative and qualitative studies, by Kmet (15). The QualSyst tool for quantitative studies is a validated generic checklist consisting of 14 items with scores from zero to two and the possibility to score ‘not applicable’. Study quality was not considered an exclusion
criterion. An assessment tool adapted from Gärtner (16) was used to determine the strength of the evidence. The
levels of evidence were defined as: (1) strong evidence, i.e., statistically significant results among 50% of the tested
relationships in longitudinal studies; (2) moderate evidence, i.e., statistically significant results in cross-sectional
studies; (3) limited evidence, i.e., statistically significant results in one study; (4) expert evidence, i.e., an indication
from one or more narrative reviews; (5) inconclusive evidence, i.e., statistically significant results in a cross-
sectional study and 50% of the relationships or less were statistically significant; and (6) inconsistent evidence, i.e.,
statistically significant results were found, but they were in different directions.

Data extraction and synthesis

As only a few articles were expected to be included, a meta-analysis of the results would not seem feasible. The
classification was presented as descriptive statistics. The study outcome results are presented in
the tabular form.
Results:
The initial search yielded 2099 potentially relevant articles. After screening of the titles and abstracts (figure 1) 14 articles that met the inclusion criteria remained for further evaluation (table 2). After full text reading we excluded seven articles: Carlo (17), Demaray (18), Jouvet (19), Keogh (20), Luyt (21), Sinha (22), and West (23). Barker published data of two studies as congress abstracts (24, 25). Until now, however, these studies have not been published in peer reviewed journals. Barker was contacted, but could not provide the unpublished data. The abstracts were not included.

Five articles met the criteria for inclusion in this review; Hermeto (26), Randolph (27), Restrepo (28), Rushfort (29) and Schultz (30). Four studies conducted on a pediatric intensive care unit also included neonates ((Randolph (27), Restrepo (28), Rushfort (29), and Schultz (30)). The authors were invited by e-mail to provide the specific neonatal data. Rushfort (29) and Restrepo (28) replied that neonates (in accordance to the WHO definition) were not included in their studies. Randolph (27) and Schultz (30) could not provide the separate neonatal data. As, moreover, the neonatal sample in their studies made up less than 75% of the total sample, their studies were excluded as well. Thus, one study met the inclusion criteria: Hermeto (26). This study was a retrospective study performed in a single center tertiary NICU in Canada. Three periods were distinguished: one year before a comprehensive ventilation protocol had been implemented (control group) and 1 and 2 years after this had been implemented. In three years, over 300 neonates were studied (n = 93/99/109 respectively). Their mean gestational age was 27 ± 2 weeks (mean ± SD) in all three periods. The median duration of MV had decreased from 18 days in the period prior to the intervention, to 5 days after one year and 6 days after 2 years. The differences in median duration of MV between the period prior to the implementation of the protocol and the periods after 1 and 2 years were significant (p<0.05). Neither the mortality rate, nor the occurrences of bronchopulmonary dysplasia, air leak syndrome and pneumonia significantly differed between these study periods. The extubation failure rate was 40%, 26% and 20%, respectively. Data analysis per birthweight group yielded similar results. Extubation failure was significantly lower in the smallest group, 500-750 grams.

In accordance with the core outcome set developed by Ringrow (13), the items HRQoL and LOS were not reported in the study by Hermeto (26).
Study quality graded with the QualSyst tool (15) resulted in an average score of 18, out of a maximum of 20 points. The quality of this study was considered good. According to the assessment with the adapted tool by Gärtner (16) the evidence of this review should be considered as limited.

Discussion:

There is limited evidence about the effectiveness of protocolized weaning for neonates. With regard to the primary outcome, only one study was included in this review (26). This study included a large group of neonates, its methodological quality was good, and the results were encouraging.

Barker (24, 25) performed a comparable study in a NICU population, the data of which were published as two congress abstracts. The use of a weaning protocol had resulted in a reduction in the mean number of ventilation days from 3.5 to 2.4 days (p=0.55). A follow-up of this study in 2015 reported a further reduction of 0.5 ventilation days (ns). Although the results are promising, it is difficult to interpret the validity of these studies: no power analysis was described and these studies have not been published in a peer-reviewed journal. Therefore these data could not contribute to this review to evaluate the effectiveness of protocolized weaning in neonates.

Despite the lack of evidence applying a protocol or guideline is one of the most frequently used practices in the weaning process, but a wide variation exists in “weaning” practices all aimed to extubate as soon as possible (4). Also different mechanical ventilation strategies can be applied (31). Currently volume targeted ventilation (VTV) is preferred compared with pressure limited ventilation (32). VTV aims to produce a more stable tidal volume in order to reduce lung injury. Spontaneous breathing trials are used to predict successful extubation in ventilated preterm infants (33-35). Also, new ventilation modalities enable to wean patients automatically (36, 37). Several ways to assess extubation readiness have been studied in neonates, using respiratory scores and measurements (38, 39).

These alternative weaning strategies could make the need for a weaning protocol less compelling. However, not only the ventilator weaning strategy itself, but the use of supportive medication such as caffeine or steroids, indication for extubation, and post-extubation support could be part of a practical comprehensive weaning protocol (40). Although extubation failure is reduced by applying nasal intermittent positive pressure ventilation instead of continuous positive pressure ventilation, no effect on chronic lung disease or mortality is achieved (41). Currently, a large multicenter RCT of sedation and weaning in 18 paediatric ICUs in the UK is underway and is actively recruiting ~14,000 children and neonates (Blackwood et al 2018: http://www.isrctn.com/ISRCTN16998143). The
weaning protocol includes daily screening for readiness to wean and a spontaneous breathing trial. The outcomes of
this RCT may provide further useful information pertinent to protocolized weaning in neonates.

Strengths of this review are the following: The review team was very familiar with this topic and the literature as
they previously had performed a Cochrane review on this topic. The extensive literature search was performed with
the help of a consultant of the medical library. The study selection was performed by several pairs separately. The
quality of the manuscripts was taken into account in the final conclusions. Validated instruments were used to assess
the methodological and strength of the studies. A Prospero protocol had been submitted in advance (ID.
CRD42016032412).

A possible limitation is that neonatal data from the eligible studies in pediatric settings could not be made available.
These could have provided extra evidence. Loosening the inclusion criteria in terms of type of studies could not
provide any additional evidence. Only the large international search sites were screened; regional or national sites
were not searched. Relevant studies in other languages than English might therefore have been missed.

Conclusion:
Due to a lack of studies there is no robust evidence to support or disprove the use of a weaning protocol for the
discontinuation of mechanical ventilation in neonates. Only one study showed encouraging results, but a new study is
underway. Studies particularly focused on neonates should be undertaken to provide specific guidance for neonatal
clinicians.

Conflict of interest:
All authors declare having no conflict of interest.
References:


### Table 1

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**Embase**

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Cochrane central

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Web-of-Science

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PubMed publisher

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newborns|infants|premature|neonates

Proquest Dissertations and theses
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clinical trials.gov
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http://www.controlled-trials.com/;
http://portal.nihr.ac.uk/Pages/default.aspx;
http://public.ukcrn.org.uk/search/; and
www.clinicaltrials.gov.

A search for theses was performed in:
www.theses.com; and

A search for conference proceedings was performed in:
• ISI Conference Proceedings (1990 to present)
• Annual Meetings of the Pediatric Academic Societies (to present),
• the European Pediatric Society (1990 to present), and
• the Perinatal Society of Australian and New Zealand (1993 to present).
Table 2

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<td>Abstract presented at the Perinatal Society of Australia &amp; New-Zealand 2014. No full text article available. Single centre prospective non-blinded cohort study. NICU setting. 111 episodes, between January and October 2013. 30% of the population were weaned using a protocol. This resulted in a reduction of duration of 2.4 vs 3.5 days. Request for the unpublished data from the authors</td>
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<tr>
<td>Barker, 2015</td>
<td>Abstract presented at the Perinatal Society of Australia &amp; New-Zealand 2015. No full text article available. Single centre retrospective cohort study, measuring the compliance with a weaning protocol and the effect on duration of ventilation. NICU setting. Continuation of the article in 2014. Compliance improved, resulting in a reduction of duration of mechanical of 1.9 vs 2.4 days (p&gt; 0.5) Request for the unpublished data from the authors</td>
<td>Included</td>
</tr>
<tr>
<td>Carlo WA, 1980</td>
<td>Single centre cohort study. NICU population. A computer algorithm versus standard interpretation of arterial blood gas values. The effect on the correction of blood gas derangements was compared.</td>
<td>excluded</td>
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<tr>
<td>Demaray W, 2007</td>
<td>Review of weaning protocols in the adult and paediatric intensive care unit. Article could not be retrieved/ found at the journal’s website</td>
<td>excluded</td>
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<td>Hermeto, 2009</td>
<td>Retrospective study, new weaning protocol for neonatal population. Development of clinical weaning guidelines for respiratory therapists. A pretest, posttest, second posttest was measured; 93, 109, and 99 neonates were included. Time to first extubation was shortened (median 5, 1.5, 1.2 days) and duration of MV (18, 5 and 6 days respectively).</td>
<td>included</td>
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<tr>
<td>Jouvet, 2013</td>
<td>Abstract of oral presentation at the European Society of Paediatric and Neonatal Intensive Care 2013, on the evidence of using weaning protocols in the paediatric and adult ICU.</td>
<td>excluded</td>
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<td>Keogh, 2003</td>
<td>Single centre intervention study, PICU population, no neonates included. Historic cohort versus prospective cohort, after implementing weaning guidelines. Both total ventilation time and length of stay were longer post-intervention (median difference: total ventilation time −15.8 hours, P&lt;0.068; and LOS −23.75 hours, P&lt;0.088).</td>
<td>excluded</td>
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<td>Luyt, 2002</td>
<td>Single-centre prospective randomized controlled trial. NICU population. 50 neonates were included. Nurse versus registrar-led weaning, with a weaning protocol. Both groups used the same protocol. Twenty-five neonates were nurse-led weaned (weaning time: 1200 min. 95% CI 621–1779) vs. 23 neonates registrar-led weaned (weaning time: 3015 min. 95% CI 2650–3380); p=0.0458. No comparison of protocolized versus non-protocolized weaning described.</td>
<td>excluded</td>
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<td>Randolph, 2002</td>
<td>Multi-centre, randomized controlled trial 182 children admitted to the paediatric intensive care unit requiring ventilator support for more than 24 hours randomly assigned; 3 excluded, 179 analysed among whom 31 neonates Request for the unpublished data from the authors</td>
<td>included</td>
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</tbody>
</table>
duration was not significantly different. Ventilator Management protocol patients had a shorter weaning time (17.5 hours; range, 1-181) than had non-protocol patients (35 hours; range, 0.5-377; P = 0.005). PICU population, no neonates were included according to the authors. pre-test patient age median range 48 (0.5-216) months; post-test 19 (0.5-252)

| Rushfort, 2005 | A single-centre randomized controlled trial to compare outcomes between medical-led and nurse-led (protocol-directed) weaning from mechanical ventilation in a PICU setting. Patient age was 2-7 weeks. No comparison between protocolized versus non-protocolized weaning was described. The study could draw conclusions because of recruitment problems. | excluded |
| Schultz TR, 2001 | Single-centre, multi-unit, randomized controlled trial 223 children requiring intubation and mechanical ventilation; 4 did not reach study end point; 219 analysed, sample includes neonates Request for the unpublished data from the authors. | included |
| Sinha S, 2006 | Describing two case studies of the weaning process in neonates. No protocol used. | excluded |
| West G, 2010 | Retrospective audit in a single centre. NICU population. Extubation failure described in relation to the adherence of the nursing guidelines during this period. | excluded |
### Checklist for assessing the quality of quantitative studies

<table>
<thead>
<tr>
<th>Criteria</th>
<th>YES (2)</th>
<th>PARTIAL (1)</th>
<th>NO (0)</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Question / objective sufficiently described?</td>
<td>x x</td>
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<tr>
<td>2  Study design evident and appropriate?</td>
<td>x x</td>
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<tr>
<td>3  Method of subject/comparison group selection or source of information/input variables described and appropriate?</td>
<td>x x</td>
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<tr>
<td>4  Subject (and comparison group, if applicable) characteristics sufficiently described?</td>
<td>x x</td>
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<tr>
<td>5  If interventional and random allocation was possible, was it described?</td>
<td>x x</td>
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<tr>
<td>6  If interventional and blinding of investigators was possible, was it reported?</td>
<td>x x</td>
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<tr>
<td>7  If interventional and blinding of subjects was possible, was it reported?</td>
<td>x x</td>
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<tr>
<td>8  Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? means of assessment reported?</td>
<td>x x</td>
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<td>9  Sample size appropriate?</td>
<td>x x</td>
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<td>10 Analytic methods described/justified and appropriate?</td>
<td>x x</td>
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<td>11 Some estimate of variance is reported for the main results?</td>
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<td>12 Controlled for confounding?</td>
<td>x x</td>
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<td>13 Results reported in sufficient detail?</td>
<td>x x</td>
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<td>14 Conclusions supported by the results?</td>
<td>x x</td>
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</tbody>
</table>

Total sum = (number of “yes” * 2) + (number of “partials” * 1)  
Total possible sum = 28 – (number of “N/A” * 2)  
Summary score: total sum / total possible sum  
Summary score: 18 / 20 0.90
Figure 1: Study inclusion flowchart

3670 articles identified through database searching
Cochrane central  136
Medline   596
Cinahl  234
Embase   1072
Web of science  436
Scopus  1137
Proquest theses  59

288 records identified through other sources:
http://www.clinicaltrials.gov  88
https://scholar.google.nl/  200

2099 records, after removing duplicates
2085 records excluded after the first assessment
14 records assessed for eligibility, of which 7 were excluded (table 2)

7 records eligible for this review:
- Two full text articles. The authors stated that neonates were not included (Restrepo, 2004; Rushfort, 2005)
- Two full-text articles, no data available for subgroups of neonates (Randolph, 2002; Schultz, 2001)
- Two studies whose data had not been made available publicly (Barker, 2014/2015)

Included in this review:
- One study with full text publication (Hermeto, 2009)