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Full length article

Trials of antenatal corticosteroids for preterm fetal lung maturity: a review of the potential for selective outcome reporting

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ABSTRACT

Objective: To measure the extent to which the evidence underpinning prenatal corticosteroids for preterm fetal lung maturity is at risk of bias due to selective outcome reporting.
Study design: Five biomedical databases (Medline, ClinicalTrials.gov, Embase, OVID and HMIC) were searched for trials published between February 2016 and September 2017.
Randomised trials of prenatal steroids for women at risk of preterm birth were identified. For each, we recorded the registration status and timing, and whether the registered primary outcome had been reported. For unregistered trials, we estimated the potential for selective outcome reporting indirectly by tabulating all reported outcomes and by comparing the first outcome reported in the methods to the first in the results section.
Results: Twenty seven trials were identified. Only three (11%) trials had been registered. All three reported their pre-specified primary outcome. Among the unregistered trials, thirteen (54%) had different first reported outcomes in the methods and results sections, and among all trials many different outcomes were reported suggesting considerable potential for selective reporting. However, the single outcome of respiratory distress syndrome, albeit defined in different ways, was reported in all but two trials. This is reassuring evidence that the beneficial effect of steroids on this outcome has not been exaggerated by selective outcome reporting.
Conclusion: We conclude that the evidence that steroids reduce respiratory distress syndrome is secure.

Introduction

Using prenatal steroids to prevent respiratory distress syndrome (RDS) in preterm babies is well established, and universally regarded as evidence-based. The Cochrane Review concluded that steroids reduce neonatal death and RDS [1], and NICE [2] recommends their administration to women suspected to be in preterm labour up to 33^{+6} weeks.

However, there are three reasons why it is worth reviewing the quality of the primary research evidence for the effectiveness of steroids for this indication. Firstly, there has been recent interest in the extent to which randomised trials of clinical interventions can have false positive results as a result of selective outcome reporting, or outcome switching; so called "P-hacking". At its simplest, if a trial of an ineffective intervention measures twenty endpoints, one is likely to be nominally statistically significant at the 5% level. If the authors fail to report the other nineteen endpoints, and to note whether the nominally significant one had been pre-specified, an ineffective intervention will be falsely declared effective. Lesser degrees of "false positives" may occur if only "promising" endpoints are reported, if multiple statistical tests are run, or if the results are inspected and the trial closed early if a nominally significant result is observed. This problem is avoided by trial registration and pre-specifying primary and secondary endpoints and the planned sample size. This was mandated by the Committee on Publication Ethics since 2004 [3] but even now is not always adhered to. Even if the trial has been registered, the pre-specified outcomes may not always be reported [4,5]. Most trials of antenatal steroids predate the regular practice of trial registration so we decided to investigate how many of them were at risk of the various types of P-Hacking.

Secondly a recent large trial [6] surprised many by showing that increasing steroid use for women in suspected preterm labour worsened perinatal outcomes. Reviewers generally concluded this was caused by many participants not being as preterm as their

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doctors believed; most pregnancies were undated. This explanation may be partially true but is weakened somewhat by another recent large trial that showed that even at 34–37 weeks, steroids reduce respiratory morbidity [7].

Thirdly there have been recent reports of possible harm caused by antenatal steroids on long term developmental and educational outcomes [13–19].

Our group have estimated the scope of P-hacking among trials of progesterone in pregnancy [8]. Here we follow similar methods to examine trials of steroids.

Materials and methods

Criteria for potentially eligible studies

The review was prospectively registered with PROSPERO (CRD42018072098).

Studies were eligible for inclusion if they, were randomised or pseudo-randomised controlled trials, published in English, and involved the administration of antenatal corticosteroids in women with threatened or actual preterm labour.

Search strategy

The primary trial report from each of the thirty trials included in the 2016 Cochrane review, were obtained and reviewed. Five biomedical databases (Medline, ClinicalTrials.gov, Embase, OVID and HMIC) were then searched for trials published since the Cochrane review (February 2016) until September 2017. The ACT trial published in 2015 [6], was also included.

Selection of studies

Titles and abstracts identified by the search strategy were assessed for inclusion by two reviewers (KW, VW). If there was disagreement about whether a report should be included, full text was obtained for that report.

For all potentially eligible studies full text copies were sought, and independently assessed for inclusion by two reviewers (KW, VW). Disagreements were resolved by discussion, and if agreement could not be reached the study was independently assessed by a third reviewer (JGT). Multiple reports of the same study were linked together.

Data extraction and data entry

Data on study quality and content were extracted onto a specifically designed data extraction form independently by two reviewers (KW, VW). Each trial was extracted onto a separate data extraction sheet. Hence, if two trials were reported in the same paper, these were extracted separately. In the few cases where full text was not available (n = 2), data were extracted from the title plus abstract. Data were entered into an Excel spread sheet, and checked. For unregistered trials, we compared the first outcome reported in the methods section to the first in the results section. For all trials we listed all outcomes reported.

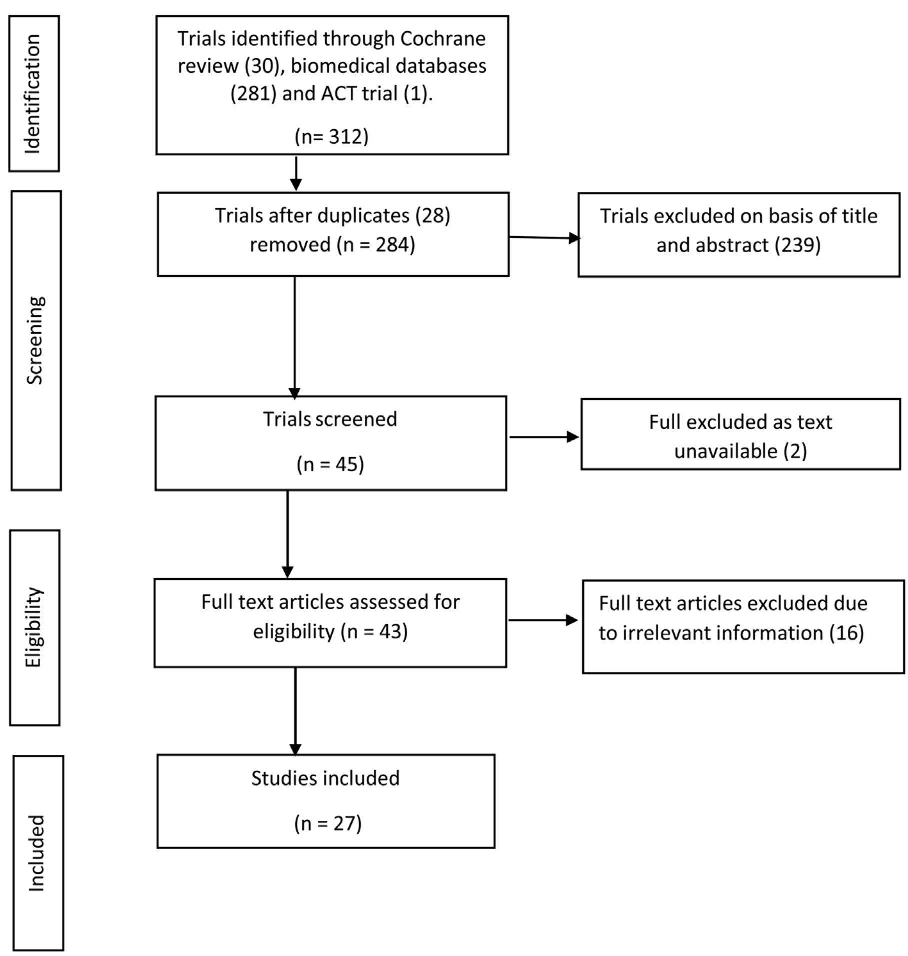

Fig. 1. Flow chart of article selection procedure for the review.

Table 1
Characteristics of studies included in this review.

Reference	No.	Population	Intervention		Control		Primary outcomes/or first outcome reported in results section	Secondary outcomes
			Type of corticosteroid	No.	Type of control	No.		
Althabe et al. [6]	4455	Women presenting <36 weeks' gestation with signs of labour, PPROM, pre-eclampsia or eclampsia, or obstetric haemorrhage	Dexamethasone	2361	No steroid	2094	28-day neonatal mortality among infants <5^{th} centile for birthweight	Maternal infection
Amorim et al. [13]	218	Women 26-34 weeks with severe pre-eclampsia	Betamethasone	110	Placebo	108	Fetal death	RDS, IVH, PDA, neonatal death, NEC, BPD, neonatal infection, GDM, MAP
Attawattanakul and Tansupswatdiku [14]	194	Singleton women $34–36^{+6}$ weeks admitted due to preterm labour	Dexamethasone	96	No steroid	98	RDS	Neonatal morbidity and mortality, Apgars <7, PPV as basic resus, admission to SNB or NICU, need for resp support (within 48 h), RDS, TTN, apnea, IVH, NEC, EONS, pneumonia, length of hospital stay, chorioamnionitis, endomyometritis, maternal length of hospital stay
Balci et al. [15]	100	Women 34–36 weeks diagnosed as susceptible to preterm delivery.	Betamethasone	50	No betamethasone	50	Apgars at 1 and 5 min	Need for resuscitation, development of RDS
Block et al. [16]	128	Women in preterm labour or with PPROM	Betamethasone	49	Saline	44	RDS	Perinatal death rate
			Methylprednisalone	35				
Carlan et al. [17]	44	Ruptured membranes at 24–34 weeks	Betamethasone	11	No treatment	13	RDS	Respirator days, NICU days, neonatal hospital days, neonatal charges in dollars
			Betamethasone and thyrotropin releasing hormone	13				
Collaborative [18]	696	Patients between 26–37 weeks at high risk of premature delivery	Dexamethasone	349	Placebo	347	RDS	Fetal and neonatal death rate, severe RDS, abnormal outcomes at 40 weeks, postpartum infection, postpartum complications (hypertension or hypersensitivity reaction), infection in infants, duration of neonatal hospital stay, RDS
Delibas et al. [10]	40	Women diagnosed with mild preeclampsia 28–34 weeks	Betamethasone	20	Normal saline	20	Biophysical profile score	Fetal tone, non-reactive, non-stress, fetal body movements, fetal breathing movements, umbilical artery Dopplers, MCA dopplers
Dexiprom [19]	204	Women with PPROM 28–34 weeks or estimated fetal weight 1–2 kg if gestational age unknown	Dexamethasone	102	Placebo	102	Chorioamnionitis	APH, postpartum sepsis, perinatal death, RDS, mechanical ventilation, NEC, neonatal infection at <72 h
Doran et al. [20]	132	Women with unplanned premature labour, spontaneous rupture of membranes, and planned premature delivery because of fetomaternal disease between 24–34 weeks	Betamethasone	70	Placebo	62	Stillbirth	Neonatal deaths, RDS.
Ernawati et al. [11]	44	All patients with preterm preeclampsia (30–34 weeks)	Dexamethasone and 7 days of methylprednisalone	22	Dexamethasone and 7 days of placebo	22	Time interval between entry and delivery	Maternal complications, maternal death, maternal postpartum length of stay, Apgars <7, perinatal death, RDS, IVH, sepsis, need for mechanical ventilation, duration of NICU admission, head circumference at 6 months, developmental delay at 6 months
Gamsu et al. [21]	251	Gestation judged to be <34 weeks and the women was in spontaneous labour or required preterm delivery for obstetric reasons	Betamethasone	126	Placebo	125	Intrauterine infection	Asphyxia, resuscitation, jaundice, hypoglycaemia, clinical signs of infection, RDS, stillbirth, neonatal deaths
Garite et al. [22]	77	All patients with intact membranes between $24–27^{+6}$ weeks gestation who were in premature labour or otherwise	Betamethasone	36	Placebo	41	Incidence and severity of RDS	Chorioamnionitis, endometritis, stillbirth, neonatal deaths, PDA, IVH,

Table 1 (*Continued*)

Reference	No.	Population	Intervention		Control		Primary outcomes/or first outcome reported in results section	Secondary outcomes
			Type of corticosteroid	No.	Type of control	No.		
		judged likely to be delivered within the ensuing week, but not within 24 h						neonatal sepsis, duration of neonatal hospital stay
Goodner [23]	92	Any pregnant women expected to deliver <34 weeks	Betamethasone	47	Placebo	45	RDS	Transient tachypnoea, neonatal mortality rate
Gyamfi-Bannerman et al. [7]	2827	Singleton pregnancy 34–36^{+5} weeks at high risk for delivery during the late preterm period	Betamethasone	1427	Placebo	1400	A neonatal composite of treatment required or stillbirth or neonatal death <72 h of age	
Kari et al. [24]	157	Threatened preterm delivery between 24–31^{+6} weeks due to uterine contractions and documented cervical changes, or because of severe pre-eclampsia with intact fetal membranes	Dexamethasone	77	Placebo	80	Neonatal mortality	Neonatal morbidity, IVH, PTL, RDS, oxygen requirements in 1st day, death, retinopathy, GI complications (NEC or ulcers), early or late neonatal sepsis, requirement for surfactant, PDA, duration of ventilatory support, duration of oxygen requirement, neonatal survival at 28 days, chronic lung disease at 28 days, survival without chronic morbidity, MAP
Lewis et al. [25]	77	Patients with preterm PROM at 24–34 weeks gestation	Betamethasone	38	No steroid	39	RDS	Latency period, endometritis, intraamniotic infection, neonatal infectious morbidity, neonatal death
Liggins and Howie [26]	266	Women in premature labour at 24–36 weeks or in whom premature delivery <37 weeks was planned because of an obstetric complication	Betamethasone acetate mixed with Betamethasone phospate	144	Cortisol acetate (as control)	122	Perinatal mortality	RDS, IVH at necropsy, survival at 28 days, puerperal pyrexia, lactation, fetal or neonatal infection, neonatal death from pneumonia, Apgars at birth, hypoglycaemia, jaundice, diarrhoea
Morales et al. [27]	165	Patients admitted with a singleton pregnancy between 26–34 weeks of gestation complicated by premature rupture of membranes	Betamethasone and ampicillin	43	Control	41	Chorioamnionitis/ intraamniotic infection	IVH, sepsis, NEC, PDA, survival, RDS, mean duration of mechanical ventilation, incidence of BPD
			Betamethasone	44				
			Ampicillin	37				
Nelson et al. [28]	68	All patients referred to hospital between 28–34 weeks' with ruptured membranes confirmed by fern test	Betamethasone and tocolytics	22	No tocolytics or steroid	24	Maternal sepsis	Latency period, neonatal days in hospital, hyaline membrane disease, neonatal deaths, neonatal sepsis
			Tocolytics	22				
Parsons et al. [29]	45	Patients between 25–32 weeks gestation with ruptured membranes and <4 cm dilatation.	Betamethasone	23	No steroid	22	Maternal morbidity	Neonatal sepsis, hyaline membrane disease, perinatal death
Porto et al. [12]	320	Women at 34–36 weeks of pregnancy at risk of imminent premature delivery	Betamethasone	163	Saline	157	Respiratory disorders (RDS and TTN)	Type of delivery, gestational age at birth, birth weight, Apgar scores at one and five minutes, treatment with exogenous surfactant, ventilatory support, admission to NICU, hypoglycaemia, jaundice, PDA, neonatal sepsis and neonatal morbidity (any one of the respiratory complications or any other morbidities) and duration of stay in hospital and death
Qublan et al. [30]	139	All singleton pregnancies between 27–34 weeks of gestation complicated by PROM	Dexamethasone	72	No steroids	67	RDS	NEC, IVH, duration of hospital stay, neonatal infectious morbidity, endometritis, perinatal mortality, Apgar ≤7 at 1 and 5 min
Shanks et al. [31]	25	Women with singleton gestations between 34–36^{+6} weeks with an immature TDx-FLM-II test	Betamethasone or Dexamethasone	10	No treatment	15	Fetal lung maturity (TDX-FLM-II level >45)	Increase in TDX-FLM-II level, NICU admission, maternal complications
Silver et al. [34]	75		Dexamethasone	39	Normal saline	36	RDS	

Data analysis

We described the flow of studies through the review, with reasons for being removed or excluded, using the PRISMA guidance [9]. Characteristics of each study were described and tabulated. No statistical analyses were anticipated.

Results

We obtained all references from the Cochrane systematic review [1]. Thirty full text copies were sought. Two full text copies were unavailable (one in Persian, one in French). Four studies were excluded. Twenty four of the available full text copies were eligible for inclusion. The ACT trial [6] was included too.

Our database search between Feb 2016 and Sep 2017 identified 281 records, of which 28 were duplicates, giving 253 (Fig. 1). Full text copies were sought for 18 records. No full text copies were unavailable. Of those full text copies, two were identified as eligible [10,11]. In total 27 studies were included (Table 1).

No single outcome measure was reported in the majority of trials although RDS was the most common primary outcome reported 12 (38%) (Table 1). The definitions used in individual outcome measures varied widely making comparison between studies problematic (Table 2).

Only three (11%) trials were registered [6,7,12] (Table 3), thus there was potential for selective outcome reporting amongst the included unregistered trials. Thirteen (54%) of the trials demonstrating a discrepancy in primary outcome (or first reported outcome) reporting between the methods and results sections of the same paper (Table 4).

Comment

Main findings

The majority of randomised controlled trials of antenatal corticosteroids for accelerating fetal lung maturity were unregistered and reported many different outcomes, giving prima facie evidence that they were susceptible to selective outcome reporting. The original trials supporting use of antenatal corticosteroids to reduce respiratory distress syndrome were unavoidably rarely registered because of the era in which they were conducted. However one outcome, respiratory distress syndrome, was reported by all but two trials, albeit defined in different ways, suggesting that for this endpoint selective outcome reporting is unlikely and the beneficial effect of steroids on RDS is secure. However the large number of other outcomes reported which vary widely between trials means that, in the absence of an individual patient data meta-analysis, there is considerable potential for selective outcome reporting, and therefore reported effect sizes are probably exaggerated.

Strengths and limitations

A comprehensive search was performed and the review was prospectively registered. To our knowledge this is the first study examining this aspect of the methodological rigour of randomised controlled trials of antenatal corticosteroids for fetal lung maturity, namely comparing outcomes reported in the registration of the trial with those reported in the trial publication.

Interpretation

Recent trials of antenatal corticosteroids to improve perinatal outcomes have had conflicting results [6,7]. Although the fact that RDS was reported in all but two trials suggests that the effect of steroids on this outcome is secure we identified considerable potential for selective reporting of other outcomes. It is therefore possible that the effect sizes of steroids on these secondary outcome is exaggerated. Ideally the raw data for the trials would be obtained and an individual patient data meta-analysis conducted. However, it is probably too late for most of the larger historical trials. This highlights the need for registration of clinical trials prior to recruitment of the first trial participant for full transparency of outcome selection and also a need for international uniformity in the definitions of key outcomes reported in clinical trials which is

Table 1 (*Continued*)

Reference	No.	Population	Intervention		Control		Primary outcomes/or first outcome reported in results section	Secondary outcomes
			Type of corticosteroid	No.	Type of control	No.		
		Hospitalized women who were at risk for delivery of viable infants in the gestational age range of interest (24–29 weeks)						Condition at birth, severity of RDS, duration of oxygen use, duration of ventilatory requirement, bronchopulmonary dysplasia, pneumothorax, PDA, NEC, IVH, retinopathy of prematurity, death, IVH severity in singletons
Taeusch et al. [32]	127	Women with an estimated gestation of $\leq 33^{+6}$ weeks in premature labour, or with PPROM, or with cervix dilated <5 cm. Women >33 weeks pregnant were eligible if they had a L/S ratio <2, or had had an infant with RDS	Dexamethasone	56	Normal saline	71	RDS	Severity of RDS, deaths during hospitalization, maternal infection, neonatal infection, apnoea, hyperbilirubinaemia, chronic lung disease/ BPD, intracranial haemorrhage
Teramo et al. [33]	74	Gestation 28 + 0 – 35 + 6, cervical dilatation at admission of less than 4 cm, no precipitous progression of labour upon initial observation of up to 12 hr, no signs of preeclampsia or diabetes mellitus.	Betamethasone	36	Normal saline	38	RDS	Gastric aspirate, maternal plasma cortisol, infant plasma cortisol

Table 2
Variation in definitions of RDS used in individual studies.

Definitions of RDS	Althabe et al. [6]	Amorim et al. [13]	Attawattanakul and Tansupswatdiku [14]	Balci et al. [15]	Block et al. [16]	Carlan et al. [17]	Collaborative [18]	Dexiprom [19]	Doran et al. [20]	Gamsu et al. [21]	Garite et al. [22]	Goodner [23]	Gyamfi-Bannerman et al. [7]	Kari et al. [24]	Lewis et al. [25]	Liggins and Howie [26]	Morales et al. [27]	Nelson et al. [28]	Parsons et al. [29]	Porto et al. [12]	Qublan et al. [30]	Shanks et al. [31]	Silver et al. [34]	Taeusch et al. [32]	Teramo et al. [33]	Delibas et al. [10]	Ernawati et al. [11]
Progressively increasing dyspnea and other signs of respiratory distress, oxygen requirement at 24 h after birth, and characteristic radiologic features		+																									
Grunting, flaring, tachypnea >60/min, retraction, and/or supplemental oxygen requirement sustained >2 h after birth			+																								
Respiratory difficulty that necessitated mechanical ventilation support, including need to provide continuous positive airway pressure which was necessary during the first hour of life and lasted for at least 24 h and typical radiological findings of the lung				+																							
Respiratory distress of sufficient severity to require placement on the mechanical ventilator or continuous positive airway pressure, and each case was confirmed radiologically					+																						
Hyaline membrane disease was considered when rapid breathing began at or immediately after birth, with cyanosis or low PaO2, and diffuse, fine granular densities on the chest radiograph. Respiratory distress syndrome severity was evaluated through oxygen and ventilatory support needs and duration																											
No definition of RDS	+					+						+															
Standard clinical, radiologic, and blood gas findings. These include chest retraction, grunting, cyanosis, increased ambient oxygen requirement, hypercarbia, and a ground-glass appearance on chest x-ray with air bronchograms and elevated diaphragms.							+																				
Central cyanosis on room air and one of: tachypnoea, recession, or expiratory grunting								+																			
Tachypnea (f>60 for >1hr). Dyspnea: intercostal, subcostal or seesawing of the chest wall and abdomen and a sterna bulge or recession, with flaring of the alae nasiae, and an expiratory grunt. Poor alveolar air entry, harsh bronchial breathing, and diffuse rales on auscultation.									+																		

Table 2 (*Continued*)

Definitions of RDS	Althabe et al. [6]	Amorim et al. [13]	Attawattanakul and Tansupswatdiku [14]	Balci et al. [15]	Block et al. [16]	Carlan et al. [17]	Collaborative [18]	Dexiprom [19]	Doran et al. [20]	Gamsu et al. [21]	Garite et al. [22]	Goodner [23]	Gyamfi-Bannerman et al. [7]	Kari et al. [24]	Lewis et al. [25]	Liggins and Howie [26]	Morales et al. [27]	Nelson et al. [28]	Parsons et al. [29]	Porto et al. [12]	Qublan et al. [30]	Shanks et al. [31]	Silver et al. [34]	Taeusch et al. [32]	Teramo et al. [33]	Delibas et al. [10]	Ernawati et al. [11]
Central cyanosis (of warm parts and mucus membranes) while breathing air. Tachycardia of 140 - 160 bpm and slight cardiac enlargement. Deficiency of lung surfactant and a low L/S ratio in tracheal fluid or amniotic fluid. Characteristic x-ray film.																											
The persistence for >6h of respiratory distress including nasal flaring of the nostrils, grunting, rib recession and tachypnoea (> 60 breaths /min), central cyanosis and need for supplemental oxygen. A characteristic chest radiograph demonstrating diffuse fine granularity, a positive air bronchogram and small lung volumes were preferred for confirmation of the diagnosis										+																	
Clinical signs and tachypnea and retractions, supplemental oxygen therapy for at least 24 h, and a chest x-ray film consistent with hyaline membrane disease.											+																
The presence of clinical signs of respiratory distress (tachypnea, retractions, flaring, grunting, or cyanosis), with a requirement for supplemental oxygen with a fraction of inspired oxygen of more than 0.21 and a chest radiograph showing hypoaeration and reticulogranular infiltrates.													+														
Typical chest radiograph changes and requirement of supplemental oxygen for at least 48 h or requirement of exogenous human surfactant therapy														+													
Diagnosis made clinically by a neonatologist and required intubation with oxygen therapy and the classic "ground glass" appearance on a chest radiograph															+												
Clinical signs of grunting respirations and chest retraction present during the first three hours and persisting beyond the first six hours after delivery, and a radiological pattern of having fine generalized granularity of lung fields with air bronchogram																+											
Characteristic radiologic findings, need for increasing respiratory																	+										

support, and clinical assessment by the attending neonatologist.										
The diagnosis of hyaline membrane disease was based on an oxygen requirement greater than 30% at 48 h, evidence of grunting, retractions, and tachypnea (rate greater than 60 per minute) at 12–24 h, and radiographic evidence as judged by a pediatric radiologist.	+									
Evidence of hyaline membrane disease based on ventilatory requirements and chest x-ray findings.		+								
The presence of respiratory distress for >2 h after birth and characterised by tachypnoea, expiratory grunting, chest wall retractions, flaring of the nostrils, cyanosis, and a growing need for oxygen and radiological evidence of diffuse reticulogranular infiltrate			+							
Characteristic radiological findings and clinical assessment by the attending pediatrician.				+						
No definition of RDS					+		+		+	+
An oxygen requirement after 24 h of life along with serial chest roentgenographic findings (reticulogranular pattern), a compatible clinical course, and specific ventilatory requirements.						+				
Clinical criteria (tachypnea, retractions, grunting, and cyanosis) and typical radiological changes in the x-ray pictures of the lung, persisting over 24 h.								+		

Table 3
Comparison between outcomes stated in the study registration and published paper.

Author, year	Registration	Sample size (registry/ paper)	Primary outcome in registry	Primary outcome in paper	Secondary outcomes in registry	Secondary outcomes in paper
Althabe et al. [6]	Prospectively registered March 2010	Registry: 6214	28-day neonatal mortality among infants <5th percentile for birthweight	28-day neonatal mortality among infants <5th percentile for birthweight	Not recorded	Maternal infection
	'Clinical Trials' NCT01084096	Paper: 4455				
Gyamfi-Bannerman et al. [7]	Prospectively registered October 2010	Registry: 2800	Composite outcome of need for respiratory support in the first 72 h; stillbirth, or neonatal death (less than 72 h of age)	Composite outcome of need for respiratory support in the first 72 h stillbirth, or neonatal death (less than 72 h of age)	Maternal outcomes: chorioamnionitis; postpartum endomyometritis; delivery prior to steroids completion; time in hours from initial dose to delivery; length of labour; mode of delivery; indication for delivery; length of stay	Maternal outcomes: chorioamnionitis; endometritis; delivery before completion of the course of glucocorticoids; and length of hospitalization
	'Clinical Trials' NCT01222247	Paper: 2831				
					Neonatal outcomes: major respiratory morbidity; respiratory distress syndrome; neonatal composite (TTN, RDS, and apnea); need for immediate resuscitation after birth; surfactant use; chronic lung disease (BPD); NEC; morbidity composite (RDS, IVH, and NEC); birth weight; hypoglycaemia; hyperbilirubinemia; feeding difficulty; hypothermia; neonatal infectious morbidity; seizures/ encephalopathy; length of hospital stay; infant re-hospitalizations	Neonatal outcomes: composite of severe respiratory complications; stillbirth or neonatal death within 72 h after delivery; RDS; TTN; apnea; BPD; surfactant administration; resuscitation at birth; hypoglycaemia; feeding difficulty; hypothermia; NEC; IVH grade 3 or 4; neonatal sepsis; pneumonia; death before discharge
Porto et al. [12]	Prospectively registered May 2008	Registry: 320	Neonatal respiratory distress	Neonatal respiratory disorders (RDS or TTN)	Duration of neonatal hospitalization; neonatal oxygen requirement; neonatal sepsis; neonatal death	Type of delivery; gestational age at birth; birth weight; Apgar scores at 1 and 5 min; treatment with exogenous surfactant; ventilatory support; admission to intensive care; neonatal hypoglycaemia; neonatal jaundice; persistence of ductus arteriosus; neonatal sepsis; neonatal morbidity; duration of stay in hospital; death
	'Clinical Trials' NCT00675246	Paper: 320				

Table 4
For unregistered trials, reporting of primary outcome in the published paper.

Reference	Primary outcome (or first reported outcome)		
	Abstract	Methods	Results
Amorim et al. [13]	RDS	RDS	RDS
Attawattanakul and Tansupswatdiku [14]	RDS	RDS	RDS
Balci et al. [15]	Apgar score	Apgar score	Apgar score
Block et al. [16]	RDS	RDS	RDS
Carlan et al. [17]	–	–	RDS
Collaborative [18]	RDS	RDS	Fetal and NN death rate
Dexiprom [19]	Chorioamnionitis	Chorioamnionitis	Chorioamnionitis
Doran et al. [20]	RDS	RDS	Stillbirth
Gamsu et al. [21]	RDS	Apgars at 1 and 5 min	Intrauterine infection
Garite et al. [22]	RDS	RDS	Maternal infection
Goodner [23]	RDS	–	–
Kari et al. [24]	RDS	Chorioamnionitis	Mortality
Lewis et al. [25]	Neonatal infectious morbidity	Intra-amniotic infection	Endometritis
Liggins and Howie [26]	Early NN mortality	RDS	Perinatal mortality
Morales et al. [27]	RDS	RDS	Chorioamnionitis
Nelson et al. [28]	Maternal hospital stay	Hyaline membrane disease	Maternal sepsis
Parson et al. [29]	–	Hyaline membrane disease	Maternal morbidity
Qublan et al. [30]	RDS	IVH	RDS
Shanks et al. [31]	TDX-FLMII levels	TDX-FLMII levels	TDX-FLMII levels >45
Silver et al. [34]	RDS	RDS	Condition at birth
Taeusch et al. [32]	RDS	RDS	RDS
Teramo et al. [33]	RDS	RDS	RDS
Delibas et al. [10]	Total biophysical profile scores	BPP score	BPP score
Ernawati et al. [11]	Entry to delivery interval	Length of expectant management	Time interval between entry and delivery

the focus of the COMET Initiative for developing core outcome sets in health care (www.comet-initiative.org/).

Conflict of interest

None declared.

Role of the funding source

None.

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None

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