Association of maternal tocolysis or antenatal corticosteroids with cerebral palsy: a study protocol

Charles S. Algert, Christine L. Roberts, Jonathan M. Morris, Sara Kenyon, Peter Brocklehurst

**Study Investigators**
Jonathan M. Morris¹,²
Sara L. Kenyon³
Christine L. Roberts¹,²
Charles S. Algert¹,²
Peter Brocklehurst⁴

1 Clinical and Population Perinatal Health Research, Kolling Institute, Northern Sydney Local Heath District, Sydney, New South Wales 2065, Australia
2 Sydney Medical School Northern, University of Sydney, Sydney, New South Wales, Australia
3 Institute of Applied Health Research, University of Birmingham, UK
4 Birmingham Clinical Trials Unit, Institute of Applied Health Research, University of Birmingham, UK

**Funding:** The Research Foundation, Cerebral Palsy Alliance PG3815

Protocol finalised: 1 August 2017
## List of Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>aOR</td>
<td>adjusted odds ratio</td>
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<tr>
<td>CI</td>
<td>confidence intervals</td>
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<tr>
<td>CP</td>
<td>cerebral palsy</td>
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<tr>
<td>GP</td>
<td>general practitioner</td>
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<td>GTN</td>
<td>glyceryl trinitrate</td>
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<td>ICU</td>
<td>intensive care unit</td>
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<tr>
<td>NEC</td>
<td>necrotising enterocolitis</td>
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<td>NHS</td>
<td>National Health Service (UK)</td>
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<tr>
<td>NICU</td>
<td>neonatal intensive care unit</td>
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<td>NSTS</td>
<td>National Strategic Tracing Service (UK)</td>
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<td>NSW</td>
<td>New South Wales</td>
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<td>OCS</td>
<td>ORACLE Children Study</td>
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<td>ONS</td>
<td>UK Office of National Statistics</td>
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<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>PPROM</td>
<td>preterm prelabour rupture of membranes</td>
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<td>SPL</td>
<td>spontaneous preterm labour</td>
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<td>TPL</td>
<td>threatened preterm labour</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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SUMMARY

Cerebral palsy (CP) is the most common developmental disorder associated with lifelong motor impairment and disability. Although severe intrapartum hypoxia/ischaemia during birth may be instrumental in the causal pathway leading to cerebral palsy this accounts for only 10% of cases. Antenatal exposures that lead to cerebral palsy are, therefore, important to understand, particularly those that are modifiable. This application seeks to determine whether antenatal exposure to medications to prevent uterine contractions (tocolysis) and assist lung maturation (corticosteroids) have any association with cerebral palsy, particularly in pregnancies presenting moderately preterm. We plan to perform a secondary analysis on two large existing datasets (the ORACLE trials) of pregnancies presenting before term. If an association is found the results could have significant implications for clinical management and the direction of future research.

OUTCOMES AND SIGNIFICANCE

This international collaboration represents a unique opportunity to determine whether tocolysis and steroids are associated with the development of cerebral palsy in a broad range of preterm pregnancies. Given anecdotal reports of a trend towards the growing use of tocolysis and steroid cover in moderately and late preterm pregnancies, findings from this study could lead to significant practice change.

BACKGROUND

Cerebral palsy is a group of disorders that can involve brain and nervous system functions such as movement, learning, hearing, seeing, and thinking. It arises following injury or insult to the brain either in utero or in the early childhood period. It is the most common cause of motor disability in childhood, with a prevalence of 1.5–3 cases per 1000 births. There has been some previous research on the potential association of antenatal medications with subsequent CP. However, almost all of the children in those studies were exposed to treatment before 32 weeks gestation, when tocolysis and steroid cover is deemed a necessity. In contrast, for the ORACLE I and II trials, almost half the infants were enrolled after 32 weeks gestation and about 30% were ultimately delivered at term. Optionality of tocolysis/steroids treatment could have existed for some of these infants. This study will examine whether fetal exposure to tocolysis and/or steroids is associated with cerebral palsy in moderately as well as very preterm infants. The exposure of interest is the intention to treat with tocolysis or steroids at the time of an ORACLE participant’s entry into the trial. The clinical decision explored is whether to administer tocolysis and steroids when imminent delivery is not certain.

Previous analyses of the ORACLE trials found an association between antibiotic exposure and cerebral palsy among the ORACLE II infants. These trials were large pragmatic trials and in total recruited over 10 000 mothers. The original ORACLE studies were designed to assess whether the administration of antibiotics to women at risk of early delivery either following preterm premature rupture of the membranes (PPROM) or threatened spontaneous preterm labour (SPL) improved neonatal outcomes.

In Oracle 1

4826 women with PPROM were randomly assigned 250 mg erythromycin (n=1197), 325 mg co-amoxiclav (250 mg amoxicillin plus 125 mg clavulanic acid; n=1212), both (n=1192), or
placebo (n=1225) four times daily for 10 days or until delivery. The primary outcome measure was a composite of neonatal death, chronic lung disease, or major cerebral abnormality on ultrasonography before discharge from hospital.

In Oracle 2

6295 women with suspected or definite preterm labour with intact fetal membranes in whom there was substantial uncertainty as to whether antibiotics should be prescribed (ie spontaneous preterm labour with intact membranes and without evidence of clinical infection) were randomly assigned 250 mg erythromycin (n=1611), 325 mg co-amoxiclav (250 mg amoxicillin and 125 mg clavulanic acid; n=1550), both (n=1565), or placebo (n=1569) four times daily for 10 days or until delivery, whichever occurred earlier. The primary outcome measure was a composite of neonatal death, chronic lung disease, or major cerebral abnormality on ultrasonography before discharge from hospital

The findings of these studies were that erythromycin given for up to 10 days to women with PROM led to a modest but statistically significant reduction in adverse short-term neonatal outcomes in singletons. In contrast, in ORACLE II, the administration of antibiotics to women in spontaneous preterm labour produced no benefit. In ORACLE II, the difficulty of diagnosing preterm labour accurately was also shown by the fact that 63.5% of women delivered after 37 weeks' gestation, despite being recruited much earlier in pregnancy.

Having established short term indications for antibiotic use in women presenting at risk of preterm birth, a second set of studies (the ORACLE Children Studies [OCS]) were conducted to ascertain the long term outcomes of the babies in these studies.6,7 These studies began in 2002 and sought follow-up information for surviving infants at 7 years of age from women who were recruited to the ORACLE trials in the UK including: 4378 infants who were born to 4148 women with PPROM who completed ORACLE I and 4473 infants who were born to 4221 women with threatened preterm labour in ORACLE II.6,7 In the original trials, women were informed of the intention to do a subsequent follow-up assessment when they gave written informed consent. Children were traced with the help of the UK Office of National Statistics (ONS) and by contact with their family doctors (general practitioners; GPs). Details of deaths and families who moved out of the UK were notified by ONS. The families of children who had been adopted, were in foster care, or had emigrated were not contacted.

Contact details of surviving children were obtained from the National Health Service (NHS) National Strategic Tracing Service (NSTS). If no response was obtained to an invitation letter, the child's GP was contacted to check details and possible reasons for non-response (eg, the child was currently in care or was a non-English speaker). Translations of all study materials were available. For those children who were not 7 years of age at the initial invitation, contact was maintained from 2001 onwards with birthday cards, newsletters, and change of address cards, and via a website. When the child was 7 years old their current address was confirmed with ONS and the GP. An information leaflet was sent to the parents, and 2 weeks later the study questionnaire was sent. If no response was obtained, contact details were checked with the GP and a reminder letter was sent by registered post to the parents or carers of the child during the week of the child's 7th birthday. If no response was forthcoming, 3 weeks later, a final letter was sent or telephone contact was made.

The primary outcome of the OCS was defined as the presence of any level of functional impairment (severe, moderate, or mild) derived from the mark III MAHS classification system8 within any of the individual attributes of vision, hearing, speech, ambulation,
dexterity, emotion, cognition, or pain. Each attribute has either five or six defined levels of impairment, ranging from normal function to severe dysfunction. These have been classified further into none, mild, moderate, or severe levels of severity for the individual attributes from the standard algorithms available within the HUI coding/procedure manual. The overall level of functional impairment was determined by their worst score on any attribute.

For children whose mothers had PPROM, the prescription of antibiotics seemed to have little effect on the health and educational attainment of children at 7 years. This was unexpected. It would have been assumed that the early benefit would improve longer term clinical outcomes for these children.

For children whose mothers had spontaneous preterm labour the prescription of erythromycin (with or without co-amoxiclav) was associated with an increase in the proportions of children with any level of functional impairment from 38% to 42% (OR 1.18, 95% CI 1.02–1.37). Similarly proportions of children with cerebral palsy increased from 1.7% to 3.3% (OR 1.93, 95% CI 1.21–3.09) associated with erythromycin and from 1.9% to 3.2% (OR 1.69, 95% CI 1.07–2.67) with co-amoxiclav. There was a suggestion that more children who developed cerebral palsy had been born to mothers who had received both antibiotics.

Comparing the long term outcomes between the two ORACLE studies is intriguing. Whilst not being a randomised comparison the following observations are particularly pertinent which are abstracted from the original Lancet publications:

1. The incidence of cerebral palsy is highest in the babies that were born having been exposed to antibiotics with intact membranes
2. This incidence of cerebral palsy is higher following exposure to antibiotics with intact membranes than for those babies who received antibiotics with ruptured membranes
3. This high incidence of cerebral palsy is despite the fact that as a group those babies who received antibiotics with intact membranes were born:
   a. 3-4 weeks later
   b. weighed 800g more
   c. were half as likely to have been ventilated
   d. were half as likely to have been admitted to NICU
   e. were less likely to have had a positive blood culture, NEC or an abnormal head ultrasound.

One exposure that is markedly different between the two groups and that has not, to date, been investigated as an independent risk factor is tocolysis. Tocolysis usage was 4-5 times higher in the women who presented with threatened preterm labour (~61%) compared with ruptured membranes (~12%). Steroid use was also somewhat higher in women with threatened preterm labour (81% versus 77%). The extract from the trial entry form below details the information about tocolysis and steroids that was collected for each participant:
With strategies for preventing preterm birth largely unsuccessful, women presenting with signs and symptoms of threatened preterm labour remain a frequent clinical challenge. In these situations, tocolytic drugs are widely used in an attempt to delay or even prevent preterm birth. The primary objective of tocolytic therapy is to prolong pregnancy sufficiently to provide time for the administration of antenatal steroids to improve fetal lung maturity and maternal transport to a hospital with a NICU. Almost all infants exposed to tocolytic therapy will also be exposed to steroid therapy, although only a fraction of women who receive steroids are managed with tocolytics. The use of tocolytics is controversial, as there is no evidence to show that tocolysis improves perinatal outcomes, a conclusion that has recently been underlined by WHO. This uncertainty is reflected in divergent global practice. Some countries use minimal or no tocolysis. Use of tocolysis and steroids by centre in ORACLE was unreported but probably varied considerably. Furthermore, there is a wide range of agents used in those centres that do administer tocolysis. One of the earliest tocolytics utilized for this purpose was ethanol infusion, although this is not generally used in current practice due to safety concerns for both the mother and her baby. Other agents studied to date include magnesium sulphate, β agonists (β sympathomimetic agents: ritodrine, salbutamol, terbutaline), prostaglandin synthesis inhibitors (indomethacin, ibuprofen, sulindac), calcium channel blockers (nifedipine), oxytocin antagonists (atosiban), and nitric oxide donors (glyceryl trinitrate). Although there are 11 Cochrane Reviews of the short-term effects of tocolysis, there are few studies with long-term outcomes. An exception is EPICURE, a follow-up study of extremely preterm infants (20-25 weeks) born in UK and Ireland in 1995. EPICURE reported an independent association between tocolysis and both seriously abnormal scan findings (OR 2.02, 95%CI 1.04-3.94) and long term oxygen dependency (OR 2.53, 95%CI 1.42-4.51).

Complex interactions of a potentially hostile uterine environment and obstetric management (including antibiotics, tocolysis, corticosteroids) may expose the fetus to pathophysiological changes that lead to or prevent cerebral injury. Women who present at risk of early birth who are administered tocolytics and steroids and/or antibiotics may have a prolonged exposure to a potentially injurious environment but the fetus can also benefit from additional days of gestation and maturation. Less certain is whether there could be neurodevelopmental consequences of exposure to tocolysis or steroids. Animal studies have reported mixed results, with the possibility of protective effects or impairment. One study in humans that followed up antenatal corticosteroid exposure reported a higher rate of CP at 2 to 3 years of age among infants exposed to repeat courses of antenatal steroids compared to a single course (2.9% versus 0.5%) but this was not statistically significant as this was based on only 7 cases of CP. A similar study among earlier gestations and with higher rates of CP found no difference in the risk of CP for repeat versus single course of steroids.

We will use the rich data set within the ORACLE studies to explore hypotheses related to antenatal exposures and cerebral palsy. Importantly, the study includes pregnancies.
presenting at moderate and late preterm gestations and will be generalisable to a broader population of pregnancies than previous studies. The aim is to assess whether exposure to tocolytics and/or steroids while the fetus is still developing increases or decreases the risk of cerebral palsy or death as the primary outcome. This composite outcome is necessary as cerebral palsy and deaths are competing outcomes. The secondary outcome will be any diagnosis of cerebral palsy. Our null hypothesis is that intention to treat with tocolytics or steroids is not associated with cerebral palsy or childhood death. Alternative hypotheses are that treatment may either increase or decrease the risk of CP.

RESEARCH PLAN

We will utilise data from the ORACLE I and ORACLE II randomised trials and the follow-up ORACLE Children Studies (OCS) I and II to examine any association between tocolysis and/or steroids, and death or cerebral palsy by 7 years of age. The ORACLE studies evaluated the impact of antibiotics on pregnancy and childhood outcomes for women at risk of early birth due to preterm prelabour rupture of the membranes (ORACLE I) or suspected or definite preterm labour with intact fetal membranes (ORACLE II). The eligibility criteria were the same for both trials except with respect to the presenting condition (PPROM or spontaneous preterm labour [SPL]). In both trials antibiotics were randomized in a factorial design (erythromycin or co-amoxiclav or both or placebo). Between 1994 and 2000, women were recruited from 161 participating centres in 14 countries. For ORACLE I, 92.2% of participants were recruited in the UK and for ORACLE II 69.9% were UK recruits. Childhood follow-up was only attempted for UK-recruited participants. Because the OCS assessed childhood outcomes, only infants discharged alive from the ORACLE trials were included. Based on OCS publications, childhood deaths in the UK are fully enumerated but information on CP is only available for the 75% of children with returned questionnaires or GP/parent contact from ORACLE I and 71% from ORACLE II.

Eligibility Criteria
Children who survived the neonatal period (first 28 days of life) born to women recruited in the UK and who had any definite follow-up, including either a questionnaire response or other parent contact, or notification of death subsequent to the neonatal period. We have chosen to include ORACLE infants who were alive at the end of the neonatal period as this is a widely accepted threshold separating the perinatal period from longer term infant and child outcomes.

A flow diagram illustrating the formation of the study population will be included in the Results. A draft version of the flow diagram is attached as Figure 1.

Outcomes
Primary Outcome:
A composite of death or CP by 7 years of age. This combined variable is necessary because cerebral palsy and death are competing outcomes, some deaths could have been undiagnosed cases of CP.

Details of the OCS study methods have been published previously, and reported in the Background section of this study plan. Briefly, cases of CP were usually identified from returned OCS questionnaires. The questionnaires were sent out to families when the child
reached seven years of age. In a further follow-up study of the OCS children reported to have CP (n=93, 56% of the children with CP in OCS), all parental reported cases were confirmed by a physiotherapist. A few additional cases were identified by GP or parent contact or by death notification. Notifications of death include descriptions of the contributing causes, which could include cerebral palsy.

Secondary outcome
Any report of CP.

Exposures
Tocolysis
Information on already prescribed or definitely intended exposure to tocolysis and steroids was collected at trial entry. Type of tocolytic is important because the mechanisms of action and the potential adverse reactions differ. Specific fields in the form were provided for beta-agonists, indomethacin, and nifedipine, and an “other” drugs text field was also used. The “other” field recorded use of glyceryl trinitrate [GTN] patches and magnesium sulphate, and also some use of drugs which properly belonged in one of the specified class fields (i.e. ritodrine and intravenous salbutamol could have been ticked as beta agonists). Magnesium sulphate could have been considered as a tocolytic agent at the time of the ORACLE trials but no UK centre reported its use. No use of atosiban was recorded at any trial centre.

Although some women would have been exposed to more than one tocolytic agent, tocolysis will be categorized into mutually exclusive categories: 1) any use of beta agonist with or without other tocolysis  2) nifedipine alone  3) indomethacin alone  4) a small “other” category including any GTN patch use or any nifedipine/indomethacin combination. The beta agonists were the most commonly used tocolytic in the UK at the time of the ORACLE trials but are now less used due to their higher rate of adverse reactions. Nifedipine and indomethacin are still in use and it is desirable that any comparison be untainted by co-administration of a beta agonist or other tocolytics.

Steroids
Only available as a tick box for completed/intended treatment with steroids. There was no differentiation between betamethasone and dexamethasone, nor any indication whether a full course was completed.

Covariates for models
Factors which may be associated with CP and that exist at presentation/randomization and are available in the data sets include gestational age at trial entry, presentation (PPROM or SPL), maternal age, multiple pregnancy, cervical dilatation and sex of infant. Maternal age will be categorised as: <20, 20-34, ≥35 years. Cervical dilatation will be categorised as > 1 cm (yes or no). Where no dilatation is recorded, this will be categorised as “no”. In addition, ORACLE II found an association between antibiotic administration and CP among women with SPL. Therefore there will be separate indicators for assigned treatment with erythromycin and for assigned treatment with co-amoxiclav.

Gestational age at birth will not be a covariate in any model. The purpose of tocolysis is to prolong gestational age, gestation at birth is directly on the causal pathway to the outcomes. Thus, gestational age is a potential intermediate, not a confounder of an association between tocolysis/steroids and cerebral palsy. Gestational age at birth was unknown at the time of trial entry and is unknown at the time of any clinical decision about whether to administer
tocolysis and steroids. Only gestational age at trial entry, as noted in the preceding paragraph, will be used for gestational age adjustment. Maternal, socio-economic or pregnancy indicators other than those mentioned here were not recorded in the ORACLE I and II trial entry databases so cannot be assessed for potential confounding.

**Sample size**
Sample size is predefined by the number of children discharged from each ORACLE trial and with some follow-up (n>3,000 for each trial). We estimate that there will be 80% power to detect a CP risk of OR=1.9 or OR=0.5 associated with beta agonists, and 80% power to detect an OR=1.8 or OR=0.3 of CP risk associated with steroid treatment in the ORACLE II cohort.

**Statistical analysis**
We will compare the trial entry characteristics on key variables (eg PPROM or SPL, tocolysis, steroids, multiple pregnancy, infant sex and gestational age at birth) for infants with and without childhood follow-up information among those recruited at UK centres, and test for and report any statistically significant differences.

We will describe tocolytic use by type of medication, including use of multiple tocolytics. The distribution of tocolysis and steroid treatment and of covariate risk factors will be reported by ORACLE presentation (PPROM or SPL). No statistical testing of the characteristics of the two baseline groups is contemplated as they are known to be different study populations a priori. A draft Table 1 is attached which shows what we plan to report.

The ORACLE I and II cohorts of eligible children will initially be analysed and reported separately. However, the pregnancy eligibility criteria were the same except for presenting condition. If the adjusted effect estimates for ORACLE I and II show no evidence of heterogeneity, we will combine the trial datasets into one model with presenting condition as an added covariate, and report results for the combined data

The associations between tocolysis and steroids and the study outcomes will be examined by fitting multilevel regression models of the dichotomous primary and secondary outcomes. Recruiting centre will be the second level (hierarchical) factor in the multilevel analysis, to take account of the similarities of maternal characteristics (such as demographic and health behaviour attributes) and obstetric management practices at each trial centre (cluster effect). The SAS procedure GLIMMIX with random intercepts will be used for the multilevel analyses. Separate models will be performed for the ORACLE I and ORACLE II cohorts. The model betas and standard errors for the outcome effect estimates associated with tocolysis (and steroid) exposures for the two cohorts will be compared using a chi squared test for homogeneity of effect. If the homogeneity P value for any comparison of effects indicates a probability that both cohorts are likely to have the same population mean effect (a P value >0.50) then the ORACLE I & II cohorts will additionally be combined for that outcome. The regression model for the combined cohorts will then have an indicator for presentation (PPROM or SPL) included as a covariate. Combining the cohorts if P>0.50 is more conservative than combining the cohorts if the test for homogeneity does not fall below the usual P<0.05 criterion; it ensures that the combination of cohorts will only occur if there is at least a 50% chance that the true population risks are the same for each cohort. A draft Table 2 is attached which shows what we plan to report.
The effect estimates of the models will be adjusted odds ratios and 95% confidence intervals (95% CI). The odds ratio provides a good estimate of the RR when the outcome is not common (primary outcome is expected to be <5%).

We will perform subgroup analyses of the primary and secondary outcomes by gestational age at trial entry, categorised as either <32 weeks gestation or ≥32 weeks gestation (roughly half of ORACLE pregnancies were recruited at ≥32 weeks). These results may be summarised in the text or may be reported in tables similar to Table 2. A sensitivity analysis will be performed by including only sigletons and the first infant from any multiple gestations.

No mediation analysis involving gestational age at birth is planned since such an analysis would not provide clinically useful information. The clinical question is whether to administer tocolysis and steroids to women presenting with PPROM or threatened preterm labour; there is no certainty at the time of presentation what the actual gestational age at birth will be. Making a distinction between the effect of prolongation of gestational age, normally only 48 hours if tocolysis is effective, and the other effects of tocolysis/steroids would be irrelevant to decision making at the time of presentation. Furthermore, causal mediation analysis assumes no unmeasured confounding (common causes) in the exposure-outcome, mediator-outcome and exposure-mediator relations, and these assumptions cannot be met.32-35

DATA MANAGEMENT

Data collection and consent
All data collected for the ORACLE I, ORACLE II and OCS studies were fully consented to by the trial participants. For the original ORACLE trials, participants were informed of the intention to do a subsequent follow-up assessment when they gave written informed consent. For the follow-up OCS trials, consent for collection of specific follow-up outcomes was sought from the women who could be contacted. The OCS studies were approved by the West Midlands Multi-centre Research and Ethics Committee. Our planned analyses will only use data previously collected by the ORACLE and OCS trials including the outcome of cerebral palsy, which has been reported on in the OCS published study results.6,7,29 The distribution of antenatal tocolytics and steroids has been reported on in the ORACLE publications.4,5 No further contact with participants is necessary. The ORACLE I, ORACLE II and OCS databases have been reviewed by the UK data custodian (the Birmingham Clinical Trials Unit; contact is Sara Kenyon) and a Material Transfer Agreement with our research group has been approved. Use of these data for research will require local ethics committee approval as the study question (the exposure of interest) differs from the OCS exposure of interest (antenatal antibiotics). Tocolysis and steroids use were reported as baseline characteristics for the original trials but no association with trial outcomes was analysed. The data files necessary for the proposed analyses have been transferred via secure file transfer protocol (FTP) to the site of the planned analysis at the Clinical and Population Perinatal Health Research group at the Kolling Institute. The data were transferred as encrypted password-protected files.

Asking women for additional consent to specifically perform the proposed analyses is not feasible due to the large number of participants and the time since the original trials (recruited 1994-2000). Furthermore, this would require that the researchers access personal information.
that is not available in the deidentified datasets. In addition, a high proportion of women are likely to have moved and the resulting non−response bias would compromise the validity and generalisability of the results. Finally there is a risk of raising anxiety or other harms among women who experienced a subsequent adverse event or whose child has had an adverse event.

**Data storage**

All data files are in electronic, de-identified format and stored on a secure server in the Kolling Building at the Northern Sydney Local Health District on a password-protected local area network with access limited to the research personnel. The server cannot be accessed remotely. Accredited professional IT staff manage the server implementing standard security and access measures to prevent the loss, misuse, theft and unauthorised access of data.

**Data sharing policy**

Any sharing of data will require the consent of the UK data custodian for the ORACLE trials. Researchers with a potential project can contact Sara Kenyon ([s.kenyon@bham.ac.uk](mailto:s.kenyon@bham.ac.uk)). A study plan or protocol for a proposed analysis, which will need to contain clear scientific justification for the particular project, anticipated outputs and timelines will be required. Independent peer review of a project may be required. Approval from an institutional ethics committee for the study will also be required. Funds are required to support the data extract and transfer.
References
Table 1  Pregnancy characteristics for ORACLE 1 and ORACLE II children with post neonatal follow up.

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<th>ORACLE I (PPROM)</th>
<th>ORACLE II (SPL)</th>
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<tr>
<td>Maternal age (years)</td>
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<tr>
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<td>≥35 years</td>
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<td>Gestational age (weeks)</td>
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<td>Multiple gestation</td>
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<tr>
<td>Cervix dilatation &gt; 1 cm</td>
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<tr>
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<td>Beta agonist</td>
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<tr>
<td>Nifedipine alone</td>
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<td>Indomethacin alone</td>
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<td>None</td>
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<tr>
<td>Corticosteroids</td>
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<td>Assigned to erythromycin</td>
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<td>Assigned to co-amoxiclav</td>
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<td>Infant sex</td>
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* GTN patch or any combination of nifedipine, indomethacin or GTN patch
Table 2  Adjusted risks of primary and secondary outcomes associated with exposure to intended treatment with tocolytics and steroids at trial entry.

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<th>CP or death ORACLE I aOR (95% CI)</th>
<th>CP or death ORACLE II aOR (95% CI)</th>
<th>test of aOR’s (P value)</th>
<th>CP or death ORACLE I &amp; II aOR (95% CI)</th>
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<tr>
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<td>Nifedipine</td>
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<tr>
<td>Indomethacin</td>
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<tr>
<td>Other</td>
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<tr>
<td>None (referent)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
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</tbody>
</table>
Figure 1  Flow diagram of the formation of the study population for analysis.

ORACLE I (PPROM): 4826 women entered in trial

4809 women completed trial

5132 infants

289 neonatal deaths
372 born outside UK

no follow-up available

 infants (ORACLE I)
- questionnaires
- death notifications

ORACLE II (SPL): 6295 women entered in trial

6241 women completed trial

6710 infants

169 neonatal deaths
1987 born outside UK

no follow-up available

 infants (ORACLE II)
- questionnaires
- death notifications