Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled, double-blind trial

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Summary

Background Severe early-onset fetal growth restriction can lead to a range of adverse outcomes including fetal or neonatal death, neurodisability, and lifelong risks to the health of the affected child. Sildenafil, a phosphodiesterase type 5 inhibitor, potentiates the actions of nitric oxide, which leads to vasodilatation of the uterine vessels and might improve fetal growth in utero.

Methods We did this superiority, placebo-controlled randomised trial in 19 fetal medicine units in the UK. We used random computer allocation (1:1) to assign women with singleton pregnancies between 22 weeks and 0 days’ gestation and 29 weeks and 6 days’ gestation and severe early-onset fetal growth restriction to receive either sildenafil 25 mg three times daily or placebo until 32 weeks and 0 days’ gestation or delivery. We stratified women by site and by their gestational age at randomisation (before week 26 and 0 days or at week 26 and 0 days or later). We defined fetal growth restriction as a combination of estimated fetal weight or abdominal circumference below tenth percentile and absent or reversed end-diastolic blood flow in the umbilical artery on Doppler velocimetry. The primary outcome was the time from randomisation to delivery, measured in days. This study is registered with BioMed Central, number ISRCTN 39133303.

Findings Between Nov 21, 2014, and July 6, 2016, we recruited 135 women and randomly assigned 70 women to sildenafil and 65 women to placebo. We found no difference in the median randomisation to delivery interval between women assigned to sildenafil (17 days [IQR 7–24]) and women assigned to placebo (18 days [8–28]; p=0.23). Livebirths (relative risk [RR] 1.06, 95% CI 0.84 to 1.33; p=0.62), fetal deaths (0.89, 0.54 to 1.45; p=0.64), neonatal deaths (1.33, 0.54 to 3.28; p=0.53), and birthweight (–14 g,–100 to 126; p=0.81) did not differ between groups. No differences were found for any other secondary outcomes. Eight serious adverse events were reported during the course of the study (six in the placebo group and two in the sildenafil group); none of these were attributed to sildenafil.

Interpretation Sildenafil did not prolong pregnancy or improve pregnancy outcomes in severe early-onset fetal growth restriction and therefore it should not be prescribed for this indication outside of research studies with explicit participants’ consent.

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Introduction Severe early-onset fetal growth restriction and subsequent preterm birth are associated with a range of adverse pregnancy outcomes including fetal and neonatal death, necrotising enterocolitis, respiratory complications, neurodisability, and lifelong risks to the health of the affected child, such as obesity and hypertensive disease. No effective treatment for fetal growth restriction as a combination of estimated fetal weight or abdominal circumference below tenth percentile and absent or reversed end-diastolic blood flow in the umbilical artery on Doppler velocimetry. In normal pregnancy, trophoblasts invade and remodel maternal spiral arteries resulting in a low-resistance, high-flow placental bed circulation. Failure of this remodelling process is a predominant feature of fetal growth restriction. Retention of vasoactive smooth muscle cells within spiral arteries promotes placental under-perfusion and hypoxia-reperfusion injury. Placental perfusion is enhanced by nitric oxide (NO), which promotes vasodilatation of maternal vessels. The NO second messenger cGMP is degraded by the phosphodiesterase enzyme class. Sildenafil citrate is an inhibitor of phosphodiesterase type 5 (PDE-5), the predominant PDE type found in the reproductive tract. Sildenafil has shown promise in cohort studies and randomised studies of fetal growth restriction.
Evidence before this study
When we designed this study, antenatal treatment was not available for early-onset fetal growth restriction due to placental insufficiency. To date, management strategies involve only intensive fetal surveillance with elective delivery, done when presumed fetal acidosis or distress is evident. We hypothesised that sildenafil has the potential to increase utero-placental perfusion, resulting in improved fetal growth and wellbeing. Our previous animal and in-vitro human studies supported this concept. Our interest in the use of sildenafil for the treatment of placental ischaemic conditions first led to a small randomised controlled trial (RCT) in women with early-onset pre-eclampsia. Although pre-eclampsia did not improve, we observed an increase in the median birthweight in the sildenafil-treated group. Patients could be offered innovative therapy through formal information sharing and consenting process within the British Columbia Provincial Health Services Authority. In this setting, sildenafil treatment was included in the management of a series of ten women with severe early-onset intrauterine growth restriction and compared with 17 women who fulfilled the treatment criteria, but either declined or were not offered sildenafil. Women treated with sildenafil had fetuses with increased fetal abdominal circumference growth velocity after treatment, and these fetuses tended to be more frequently liveborn and able to survive intact to primary hospital discharge. Similar improvements in fetal blood flow have been observed in vivo and in animal models, and in ex-vivo human tissue.

Global interest in sildenafil as a potential treatment for fetal growth restriction has led to several coordinated national studies that are embedded in the Global Obstetric Network (GONet). This initiative includes prospective individual patient data meta-analysis. In this study, we aimed to report the results of the first study from this initiative—a randomised trial hypothesising that sildenafil can delay the birth of the severely growth-restricted fetus by at least 1 week by increasing blood flow to the placental bed with subsequent improvement in fetal growth and wellbeing in utero.

Methods
Study design and participants
The study was designed as a randomised controlled trial with sildenafil, or the placebo equivalent, prescribed at a dose of 25 mg three times per day. This dosage regime was based on previous studies by the collaborators on this project. We recruited participants from 19 fetal medicine units in the UK. All women had a singleton pregnancy between 22 weeks and 0 days’ gestation and 29 weeks and 6 days’ gestation with a diagnosis of fetal growth restriction and had agreed to expectant management. For the purposes of the study, we defined fetal growth restriction as a fetus with abdominal circumference or estimated fetal weight below the tenth percentile using local charts and absent or reversed end-diastolic flow in the umbilical artery on Doppler velocimetry. We excluded women from the study if they were younger than 16 years old, had a known contraindication or allergy to sildenafil, had known or suspected significant chromosomal or structural anomaly, reported current cocaine use, or had a condition which was likely to require delivery within 72 h (such as severe pre-eclampsia).

Ethical approval was given by the North East Research Ethics Committee (14/NE/0011) in the UK. Each participating site provided a site-specific approval and all participants provided written informed consent. An Independent Safety Data Monitoring Committee (ISDMC) was established to review the safety and efficacy data. The protocol was first registered on July 31, 2014, 4 months before the first patient was recruited (number ISRCTN 39133303).

Randomisation and masking
We used a web-based application to allocate treatment (1:1) with randomisation stratified by site and gestation (<26 weeks and 0 days and ≥26 weeks and 0 days).
Gestational age was confirmed by first trimester ultrasound and, in each case, the diagnosis of severe early-onset fetal growth restriction was confirmed by a fetal medicine expert having excluded fetal anatomical abnormalities. In addition, a full history was taken, measurements of maternal cardiovascular parameters (pulse and blood pressure), fetal biometry, and Doppler velocimetry were taken, and maternal venepuncture for angiogenic biomarkers was carried out at randomisation. Randomisation lists were pregenerated using randomly permuted blocks of size two and four.

All participants had a further assessment of blood pressure, pulse rate, and a blood sample taken 2 h after receiving their first oral dose. Subsequently, women were followed up within 3–4 days and at weekly intervals thereafter, or earlier when clinically indicated. The rest of clinical care was at the discretion of the local fetal medicine experts and included regular ultrasound assessment of growth and Doppler blood flow and antenatal cardiotocography. The consensus was reached that an expectant management is considered standard of care and that, whenever possible, the fetal growth restriction management would be consistent with the TRUFFLE study protocol.

Medication was overencapsulated (Sharp Clinical Services, Crickhowell, UK) to ensure that patient, clinicians, and pharmacists were masked to the study drug. All participants received oral medication, sildenafil 25 mg or placebo, three times a day. Medication was dispensed in 10 day supplies with a new supply being provided every week to ensure there was no period when medication was missed. We used pharmacy logs to monitor adherence. We stopped treatment at 32 weeks and 0 days or delivery, whichever came first. We advised women of potential side-effects and their family physician was informed by letter of trial participation.

We collected data on pregnancy outcome prospectively from the clinical maternity notes and entered them on a secure electronic database. We monitored data quality and protocol compliance regularly with both central and on-site monitoring methods.

**Outcome measures**

The primary efficacy outcome was the time from randomisation to delivery, measured in days. We chose this outcome because any safe prolongation of pregnancy is likely to be beneficial for the fetal growth-restricted fetus, with a reported daily increase in survival and both short-term neonatal adverse outcomes and neurodisability being closely correlated with gestation at birth. We considered other strong predictors of adverse outcomes in fetal growth-restricted fetuses, which include abnormal blood flow in the...
umbilical artery and estimated fetal weight below third percentile, but a consensus was reached that, given the severity of fetal growth restriction in our cohort, these other parameters would be less responsive to any potential beneficial effect of sildenafil.

Secondary outcomes included livebirths, fetal and neonatal deaths, birthweight, neonatal morbidity (any intraventricular haemorrhage, oxygen dependency at 28 days and 36 weeks corrected gestational age, necrotising enterocolitis, or retinopathy of prematurity), use of surfactant, ventilator dependency, admission to neonatal intensive care unit, time to newborn discharge, and maternal side-effects.

To elucidate the mechanism of sildenafil action, we planned to compare the changes between two randomised groups in the uteroplacental and fetal circulation assessed by Doppler ultrasound and in the concentrations of angiogenic biomarkers; placental growth factor (PIGF), vascular endothelial growth factor (VEGF), soluble endoglin (sENG), and soluble fms-like tyrosine kinase 1 (sFlt-1). Four vessels were examined serially with Doppler ultrasound, umbilical artery, middle cerebral artery, ductus venosus, and uterine artery, at least weekly from randomisation until delivery. In addition to the pulsatility index, umbilical artery end-diastolic flow, ductus venosus a-wave and bilateral uterine artery notching was recorded. We have defined an improvement or deterioration as a significant change in the Doppler findings between visits. For umbilical artery, the abnormal findings were raised pulsatility index, absent end-diastolic flow, or reversed end-diastolic flow; for middle cerebral artery, pulsatility index was either normal or low (<5th percentile); for ductus venosus a-wave was either present, absent or reversed, and for uterine artery Doppler findings were recorded as abnormal if mean pulsatility index was more than 1·45 or if bilateral notching was present.

We collected serum and plasma samples (≥2 mL) serially for 2 weeks. A maximum of six samples were taken during the antenatal period: immediately before drug administration, 2 h after, and on days 3, 7, 10, and 14, in line with a standardised operating procedure. All samples were analysed retrospectively and were not revealed to the clinicians. We determined maternal serum concentrations of sFlt-1 and PlGF (pg/mL) using the automated Elecsys electro-chemiluminescence immunoassay platform (Roche Cobas, Mannheim, Germany) and used these concentrations to calculate sFlt-1:PlGF ratio. Additional analysis of PlGF was done on baseline (pretreatment) plasma samples using the Alere Triage system (Alere, San Diego, CA, USA). We analysed maternal serum concentrations of VEGF (pg/mL) and sEng (ng/mL) using human Quantikine enzyme-linked immunosorbent assays (R&D Systems, Minneapolis, MN, USA).

Adverse events and adherence
We assessed and recorded adverse events and adherence at weekly clinical visits from recruitment to delivery. We encouraged participants to record any side-effects or adverse events that would then be reviewed and documented during each clinical visit. We assessed adherence weekly during clinical review and recorded any temporary discontinuations in treatment. We considered adherence to treatment to be good if the reported intake of tablets
was 90% or more of the total expected to have been taken between randomisation and the date of the visit.

Statistical analysis
We derived the recruitment target from audits of outcomes of severe fetal growth restriction from four participating hospitals in which potentially eligible pregnant women remained undelivered for a mean of 20 days (SD 11). To confirm that sildenafil can prolong pregnancy by 7 days, we needed to recruit a total of 104 women (a 5%, power 90%). Although we did not anticipate any loss to follow-up, we planned to recruit 112 women, which was later increased to 135 women in consultation with the ISDMC to account for lower than expected livebirths (protocol was updated). Although the power for the primary outcome increased to 94% (post-hoc calculation), this increased sample size would still not have adequate power to detect clinically important differences for most secondary outcomes.

We defined participants’ groups for analysis on an intention-to-treat basis. We presented unadjusted estimates with Kaplan Meier estimates and analysed with linear regression techniques, including the stratification factor as a main effect. We reported the treatment effect as the mean difference between groups. We determined statistical significance as p=0·05 or less. We included women randomised before week 26 and 0 days and at week 26 and 0 days or later in the subgroup analyses.

For continuous data, the analysis of secondary outcomes matched the analysis for the primary outcome. We compared binary data across treatment groups using a χ² test or Fisher’s exact test as appropriate and reported using relative risk [RR] with 95% confidence intervals. We analysed biomarker data (PlGF, sFlt-1, sENG, and sFlt-1:PlGF ratio) using repeated measures ANOVA methods including terms for time, treatment allocation, and their interaction. Model results are presented in terms of means and 95% CIs. We did all analyses with the statistical software package, R (version 3.3.3).

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. RJ, CC, and ZA had full access to the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results
We recruited 135 women between Nov 21, 2014, and July 6, 2016, from 19 fetal medicine units within the UK (figure I). 75 women were recruited before 26 weeks and 0 days’ gestation and 60 women between 26 weeks and 0 days’ gestation and 29 weeks and 6 days’ gestation. We randomly assigned 70 women to sildenafil and 65 women to placebo. None of the women withdrew their consent nor were lost to follow-up; therefore, we did not do additional per-protocol analysis.

Differences at baseline were not clinically important between the sildenafil group and the placebo group for ethnicity, age, body-mass index, parity, and pre-existing...
pre-eclampsia, but more women self-reported smoking in pregnancy in the sildenafil group than the placebo group (table 1).

The median gestation at randomisation was 24·4 weeks (IQR 24·0–27·5; table 1). At randomisation, reversed Doppler umbilical artery end-diastolic flow was detected in 44 (33%) participants (table 1). The remaining participants all had absent umbilical artery end-diastolic flow. The fetal ductus venosus a-wave was absent or reversed in eight (6%) participants (table 1). The estimated fetal weight at randomisation was 445 g (IQR 344–608; table 1). Of the 135 participants, 98 (73%) women had at least one severe Doppler abnormality detected, but no difference between sildenafil and placebo groups. In the sildenafil group, 21 (38%) of 55 participants had intraventricular haemorrhage grade 1 detected on antenatal MRI; in the placebo group, three severe adverse events occurred between the two groups, although the trial was not adequately powered for these secondary outcomes. Between-group differences were not observed in the pattern of Doppler changes in uterine arteries or the other two examined fetal vessels (umbilical artery and middle cerebral artery; table 3).

Angiogenic biomarker data did not change either over time or because of the administration of sildenafil (appendix). VEGF concentrations were found to be below the lowest assay standard (30 pg/mL) in all cases and were therefore not included in the analysis. Good adherence was reported; of the 265 recorded cycles of therapy, 257 (97%) reported that drug adherence was at least 90%. At a participant level, 130 (96%) of the 135 participants had study drug compliance of at least 90%. At a participant level, 130 (96%) of the 135 participants had study drug compliance of at least 90% for all cycles of therapy (data not shown).

Angiogenic biomarker data did not change either over time or because of the administration of sildenafil (appendix). VEGF concentrations were found to be below the lowest assay standard (30 pg/mL) in all cases and were therefore not included in the analysis. Good adherence was reported; of the 265 recorded cycles of therapy, 257 (97%) reported that drug adherence was at least 90%. At a participant level, 130 (96%) of the 135 participants had study drug compliance of at least 90% for all cycles of therapy (data not shown).

Eight serious adverse events were reported during the course of the study; none of these were attributed to sildenafil. Three (38%) were maternal hospital admissions in the placebo group; one for antepartum haemorrhage, one for being generally unwell, dizzy, and light-headed, and one following a stillbirth with drowsiness. Two neonatal severe adverse events were reported in the sildenafil group; the baby with Down's syndrome had an atrioventricular septal defect and fetal intracranial haemorrhage grade 1 detected on antenatal MRI; the other two examined fetal vessels (umbilical artery and middle cerebral artery; table 3).

Of the 135 participants, 98 (73%) women had at least one severe Doppler abnormality detected, but no difference between sildenafil and placebo groups. In the sildenafil group, 21 (38%) of 55 participants had intraventricular haemorrhage grade 1 detected on antenatal MRI; in the placebo group, three severe adverse events occurred between the two groups, although the trial was not adequately powered for these secondary outcomes. Between-group differences were not observed in the pattern of Doppler changes in uterine arteries or the other two examined fetal vessels (umbilical artery and middle cerebral artery; table 3).

The exposure to antenatal corticosteroids and magnesium sulphate given for neuroprotection was similar in both groups (table 3). Caesarean sections did not differ between the two groups (table 3), with 98% (90 of 92) of all livebirths delivered by caesarean section (table 4). Livebirth rates and neonatal deaths did not differ between treatment groups (table 4). 43 (72%) of the 60 deaths occurred in utero and 48 (80%) deaths occurred in the subgroup randomly assigned before 26 weeks (table 4). Differences were not clinically significant between groups for any other prespecified secondary outcomes (table 4).

Discussion
Sildenafil did not result in prolongation of pregnancy when administered to pregnant women with a severely growth-restricted fetus. No clinically important differences in mortality or short-term neonatal morbidity occurred between the two groups, although the trial was not adequately powered for these secondary outcomes.
We anticipated a beneficial effect on placental function if sildenafil treatment was effective, as assessed by uteroplacental and fetal Doppler studies and angiogenic biomarkers, even in the absence of a clear benefit on substantive clinical outcomes. The observed higher proportion of babies in whom Doppler findings in ductus venosus deteriorated with sildenafil treatment might have been a chance finding, but is also potentially worrying, particularly if linked to the slightly shorter randomisation to delivery interval in this group. We found no such

<table>
<thead>
<tr>
<th></th>
<th>Sildenafil group (n=70)</th>
<th>Placebo group (n=65)</th>
<th>Relative risk (95% CI)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Livebirths</td>
<td>49 (70%)</td>
<td>43 (66%)</td>
<td>1.06 (0.84 to 1.33)</td>
<td>0.62</td>
</tr>
<tr>
<td>&lt;26 weeks’ gestation</td>
<td>22 (31%)</td>
<td>15 (23%)</td>
<td>1.28 (0.80 to 2.06)</td>
<td>0.31</td>
</tr>
<tr>
<td>≥26 weeks’ gestation</td>
<td>27 (39%)</td>
<td>28 (43%)</td>
<td>0.96 (0.83 to 1.12)</td>
<td>0.59</td>
</tr>
<tr>
<td>Fetal death</td>
<td>21 (30%)</td>
<td>22 (34%)</td>
<td>0.89 (0.54 to 1.45)</td>
<td>0.64</td>
</tr>
<tr>
<td>&lt;26 weeks’ gestation</td>
<td>18 (26%)</td>
<td>20 (31%)</td>
<td>0.79 (0.50 to 1.23)</td>
<td>0.31</td>
</tr>
<tr>
<td>≥26 weeks’ gestation</td>
<td>3 (4%)</td>
<td>2 (3%)</td>
<td>1.00 (0.37 to 8.34)</td>
<td>0.26</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>37/49 (76%)</td>
<td>28/43 (65%)</td>
<td>1.23 (0.86 to 1.75)</td>
<td>0.25</td>
</tr>
<tr>
<td>&lt;26 weeks’ gestation</td>
<td>6 (9%)</td>
<td>7 (11%)</td>
<td>1.33 (0.54 to 3.28)</td>
<td>0.53</td>
</tr>
<tr>
<td>≥26 weeks’ gestation</td>
<td>4 (6%)</td>
<td>3 (5%)</td>
<td>1.33 (0.33 to 5.45)</td>
<td>0.69</td>
</tr>
<tr>
<td>Neonatal morbidity</td>
<td>520 (355-602)</td>
<td>450 (356-579)</td>
<td>0.96 (0.83 to 1.12)</td>
<td>0.59</td>
</tr>
<tr>
<td>&lt;26 weeks’ gestation</td>
<td>13/15 (87%)</td>
<td>13/15 (87%)</td>
<td>1.35 (0.79 to 2.29)</td>
<td>0.27</td>
</tr>
<tr>
<td>≥26 weeks’ gestation</td>
<td>15/28 (54%)</td>
<td>11/20 (55%)</td>
<td>1.13 (0.70 to 1.82)</td>
<td>0.62</td>
</tr>
<tr>
<td>Infants with composite perinatal adverse outcome (perinatal death or neonatal morbidity)</td>
<td>58 (83%)</td>
<td>50 (77%)</td>
<td>1.08 (0.91 to 1.28)</td>
<td>0.38</td>
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</tbody>
</table>

(Table 4 continues on next page)
adverse effect from sildenafil on the blood flow in uterine arteries, umbilical artery, or middle cerebral artery. Although we could not obtain two separate measurements for all babies, in this placebo-controlled study, the Doppler measurements were very unlikely to be systematically biased. At present, we cannot offer a plausible pathophysiological explanation for the possible adverse effect of sildenafil on the fetal blood flow in our cohort.

Our findings are in contrast with animal and several previously reported clinical studies. The sildenafil dose used in our study was based on the consensus from researchers with most experience in clinical evaluation of sildenafil in pregnancy at the time and a higher dose could possibly have been more effective. A systematic review identified 16 studies of sildenafil in human pregnancies, of which only four exceeded our daily dose of 75 mg in three divided doses. Three reports of improved uteroplacental perfusion in fetal growth restriction pregnancies used a 50 mg dose once daily and recruited women at later gestations with umbilical end-diastolic flow present in most cases. As pharmacokinetic studies of sildenafil in pregnancy are not available, it would be difficult to determine an ideal dosing schedule for future studies. More importantly, a possibility that the 25 mg dose three times daily might have a deleterious effect on blood flow in the ductus venosus would require extreme caution in any future studies with a higher dose, particularly in fetuses with absent or reversed end-diastolic flow in the umbilical artery.

Another possibility is that our definition of growth restriction included fetuses with such advanced disease that it was not possible to improve or reverse the process. We recruited more than half of the fetal growth-restricted babies before 26 weeks’ gestation and all fetuses had severely compromised umbilical circulation with absent or reversed end-diastolic flow; overall mortality was around 45%. In comparison, the average gestational age at randomisation in the study by Dastjerdi and colleagues was 35 weeks. The authors did not report the proportion of babies with absent or reversed umbilical artery food flow, but given the reported gestation, these babies would have been likely to have been delivered rather than recruited. El-Sayed and colleagues reported that only 11 (20%) of 54 babies developed absent or reversed end-diastolic umbilical artery blood flow at some point after randomisation, whereas in the study by Trapani Jr and colleagues, reversed umbilical artery blood flow was, in fact, an exclusion criterion. None of the studies reported any perinatal deaths or long-term follow-up data and it is, therefore, far too early to speculate that the reported improvements in uteroplacental perfusion in less severe fetal growth restriction at later gestation would lead to improved survival and better long-term outcomes. Although we had no firmly agreed fetal monitoring protocol or uniform triggers for delivery of compromised babies in our study, all participating units had access to fetal medicine experts, detailed Doppler assessment of fetal and uteroplacental circulation and antenatal cardiotocography. Therefore, the broad agreement of overall survival in our study with other studies that included severe early-onset fetal growth restriction with abnormal umbilical artery Doppler is not surprising. We have already started long-term follow-up for infants who survived and plan to combine our data in a prospective individual patient data meta-analysis to look for any possible long-term effect of sildenafil, particularly on neurodevelopmental and cardiovascular outcomes.

The absence of substantial changes in angiogenic biomarkers in the interval between randomisation and delivery and between the two trial groups is disappointing and consistent with clinical results. However, angiogenic markers might improve the prediction of favourable short-term and long-term outcomes and this improvement is an area that we aim to explore further. In summary, when sildenafil was administered to pregnant women with a severely growth-restricted fetus, it did not prolong pregnancy, improve survival, or reduce short-term neonatal morbidity.

**Contributors**
All authors contributed to the conception and design of the study, or the acquisition, analysis or interpretation of the data for manuscript. All authors contributed to the revision of the manuscript for important intellectual content. ZA was the principal investigator involved in the conception of the study, the design, the conduct of the study, and drafted and edited the report. AS, MAT, LCK, PNB, EDJ, AK, PvD, and ATP were involved in the conception and design of the study and contributed to the drafting and revision of the report. RJ was the trial statistician and

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<table>
<thead>
<tr>
<th>Table 4: Neonatal outcome according to treatment</th>
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<tr>
<td>Sildenafil group (n=70)</td>
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<tr>
<td>------------------------</td>
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<tr>
<td>Ventilator dependency</td>
</tr>
<tr>
<td>&lt;26 weeks’ gestation</td>
</tr>
<tr>
<td>≥26 weeks’ gestation</td>
</tr>
<tr>
<td>Ventilator days</td>
</tr>
<tr>
<td>&lt;26 weeks’ gestation</td>
</tr>
<tr>
<td>≥26 weeks’ gestation</td>
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Data are n (%), n/N (%), mean weighted difference (95% CI), or as indicated. NICU=neonatal intensive care unit.
advised on the analysis of the data and contributed to the drafting and revision of the report. CC assisted with the design and service delivery aspect of the study and contributed to the drafting and revisions of the paper. JH assisted with the service delivery and biomarker aspects of the study and contributed to the drafting and revision of the report.

Declaration of interests
PNB and LCK report a minority shareholding in Metabolomic Diagnostics, outside of the submitted work, and have patents relating to screening tests (not therapy) for pre-eclampsia issued. All other authors declare no competing interests. This report is independent research funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC–NIHR partnership. The views expressed in this publication are those of the authors and not necessarily those of the MRC, National Health Service, NIHR, or the Department of Health.

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References
5 Bardin C, Priave G, Papageorghiou A. Outcome at 5 years of age of SGA and AGA infants born less than 28 weeks of gestation. Semin Perinatol 2004; 28: 288–94.


