Dear Sir,

We were concerned and deeply disappointed to read the mis-informed comments of Symonds and Budge regarding the STRIDER Trial (1) who erroneously state that the "trial intervention resulted in 11 infant deaths due to lung related problems". In fact, just one of five funded trials of similar design was stopped following an interim analysis because of a possible excess number of cases of pulmonary hypertension in the treatment arm (REF). At least one of the authors of this letter should be aware that pulmonary hypertension is a common complication in this high-risk group of severely growth restricted pre-term new-borns. The authors should also be aware that the STRIDER UK Trial and the STRIDER Aus/NZ Trials have completed and neither found an excess of this complication in over xxx babies treated with sildenafil (2).

Secondly, the authors selectively cite just one study from 2009 (3) in support of their incorrect assertion that there is a clear signal of harm from animal studies. On the contrary, a recent meta-analysis supports the hypothesis that sildenafil improves fetal growth and maternal blood pressure regulation in animal models of fetal growth restriction and pre-eclampsia (4).

We wish to highlight comments in the Editorial (5) which accompanied publication of the UK STRIDER Trial (2). The STRIDER collaboration and the pre-planned Individual Patient Data Analysis represents a remarkable and unique collaboration that accrued national funding and ethical approvals in different countries to address an important issue and was the most effective way to do a difficult and much needed trial at scale and in an acceptable time frame.

Finally, we wish to remind the authors and the readership of this journal that, in this context, negative results are hugely important. We note, with justified frustration, the scale of the international coverage of an interim analysis, compared with the ongoing difficulty of publishing negative results from completed, well designed, large trials. Whilst it is easy for those who have never conducted such an endeavour to criticise, the STRIDER Trials were essential to prevent the persistent creep of clinical use in a non-evidence-based way.

Yours etc.

1. Symonds and Budge. BMJ 2018;362:k4007
2. Sharp A, Cornforth C, Jackson R, et al., STRIDER group. Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled, double-blind trial. Lancet Child Adolesc Health2018;2:93-102. doi:10.1016/S2352-4642(17)30173-6 pmid:30169244
3. Miller SL, Loose JM, Jenkin G, Wallace EM. The effects of sildenafil citrate (Viagra) on uterine blood flow and well being in the intrauterine growth-restricted fetus. Am J Obstet Gynecol2009;200:102.e1-7. doi:10.1016/j.ajog.2008.08.029 pmid:18845296
4. Paauw ND, Terstappen F, Ganzevoort W, Joles JA, Gremmels H, Lely AT. Sildenafil During Pregnancy: A Preclinical Meta-Analysis on Fetal Growth and Maternal Blood Pressure. Hypertension. 2017 Nov;70(5):998-1006. doi: 10.1161/HYPERTENSIONAHA.117.09690. Epub 2017 Sep 11. PubMed PMID: 28893896.
5. Smith GCS. The STRIDER trial: one step forward, one step back. Lancet Child Adolesc Health. 2018 Feb;2(2):80-81. doi: 10.1016/S2352-4642(17)30176-1. Epub 2017 Dec 7. PubMed PMID: 30169238.