To be decoded. (Mini-commentary on BJOG-19-1802.R1 & BJOG-19-1803.R1)

Zarko Alfirevic[1] and Simon Gates[2]

[1]University of Liverpool
[2]University of Birmingham Edgbaston Campus

April 28, 2020

Mini-commentary on BJOG-19-1802.R1 & BJOG-19-1803.R1

Title: **To be decoded**

Zarko Alfirevic,

Department of Women's and Children's Health, University of Liverpool

Simon Gates

Cancer Research UK Clinical Trials Unit, University of Birmingham

Email contact: Zarko Alfirevic, Zarko@liverpool.ac.uk

Randomised trials remain gold standard for evaluation of effectiveness of medical interventions. However, they are expensive, time consuming and demand huge efforts from participants, researchers and clinical services that facilitate them. Even when trials are successfully completed, peer reviewers often find them wanting. One of the most common criticisms is a 'lack of power' to tackle clinically important outcomes. Why is this happening time and again?

When an important clinical question creates an equipoise, trialists are faced with difficult choices. If they design a trial to tackle the most important (often rare) outcomes aiming to detect modest, but plausible, risk reductions from a proposed intervention, such studies are rarely feasible and very expensive forcing most funders to simply walk away. Common 'remedies' are to change the outcome to something more common and less important (often composite), or to propose an unrealistic risk reduction, sometimes in excess of 50%. Trials of magnesium sulphate for neuroprotection included in the seminal Cochrane review (Doyle LW et al. DOI: 10.1002/14651858.CD004661.pub3) that triggered changes in numerous guidelines world-wide were not an exception (Table 1).

Cerebral palsy is a rare, but devastating complication of prematurity and even a very modest reduction would, surely, be worth detecting. The problem is that even in the most 'at risk' groups, the incidence of cerebral palsy will not exceed 10%. A conventional sample size calculation estimates that to detect a 'massive' 25% risk reduction in cerebral palsy, in excess of 5,000 women would have to be randomised.

Interestingly, such a priori sample size calculations are not a feature of most published meta-analyses. Step forward Trial Sequential Analysis (TSA). The TSA is a deceptively simple concept; meta-analysis sample size needs to be increased to allow not only for the heterogeneity of included studies, but also for repeated testing when meta-analyses are being updated and therefore subjected to repeated significance testing. Interested readers can find out more from the Copenhagen Trial Unit's website - vocal proponents of this methodology (www.ctu.dk/tsa).

In their two sister papers, Wolf et al have, quite ingeniously, used TSA to determine the size of their randomised trial and, by doing so, avoided the risk of their randomised trial and updated meta analysis being criticised as 'underpowered' (Wolf H et al. BJOG 2020 xxxx (RCT); Wolf H et al. (BJOG 2020 xxxx (SR & MA). Could this concept be a methodological 'game changer' in perinatal trials?

The concept of TSA has been widely criticised, and a Cochrane Collaboration expert panel recommended against its use (https://methods.cochrane.org/sites/default/files/public/uploads/tsa_expert_panel_guidance_-and_recommendation_final.pdf). Key criticisms are, first, that decision-makers require a summary of the currently available evidence and this should not depend on past and future updates. Second, TSA focuses only on statistical significance. Interpretation of meta-analysis should be based on the estimates of the treatment effect and its uncertainty, rather than whether an arbitrary significance threshold is passed. Third, the ways that evidence accumulates in systematic reviews and individual trials are fundamentally different. Review updates are not equivalent to trial interim analyses; updates are not pre-planned and their number cannot be determined in advance. Furthermore, reviews address multiple clinically-relevant effects on several outcomes or subgroup analyses, which need to be integrated into an overall conclusion. The Cochrane expert panel concluded: "Any sequential adjustment procedure is necessarily based on a particular instance of the evolution of evidence that applies to a limited context and cannot satisfy the requirements of all decision makers."

Table 1. Key features of randomised trials of $MgSO_4$given to pregnant women for prevention of cerebral palsy in infants born preterm

Trial	**Primary outcome**	**Anticipated reduction from MgSO4**	**Number of**
MAGNET (1)	Neonatal intraventricular haemorrhage	18.9% to 4.4%	149
ACTOMgSO4 (2)	Cerebral palsy	10% to 5%	1062
PREMAG (3)	White matter injury	8% to 4 %	573
MAGPIE (4)	Neuroprotection for the mother	Not applicable	1544
Rouse et al. (5)	Stillbirths, death by 1 year or cerebral palsy	14% to 9.8%	2241

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