Response to:

Challenges of modulating the risk of bronchopulmonary dysplasia in clinical trials
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Title: Challenges of modulating the risk of bronchopulmonary dysplasia in clinical trials – Authors' Reply

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We thank Thomas and colleagues for their comments.

AZTEC used prophylactic azithromycin aiming to improve survival without development of chronic lung disease of prematurity (CLD). The primary outcome was chosen after significant consideration, including ability to measure it in a large multi-centre RCT[1] and in keeping with other recent large neonatal trials[2]. We believe that parents and clinicians value a treatment that improves survival without moderate/severe CLD, acknowledging different prognosis between moderate and severe CLD. Whilst we do not dispute existence of alternative primary outcomes, with several defined after AZTEC started, each has strengths and weaknesses. Therefore, given concerns about definitions of CLD, we are following up the recruited infants at one/two years of age to assess their respiratory status[3]. Likewise, although we do not dispute differing cardiological phenotypes of CLD, we are not aware of data of azithromycin impacting these. Disappointingly, trials targeting cardiovascular events including patent ductus arteriosus or pulmonary hypertension in the neonatal period to prevent development of CLD have also been unsuccessful[2,5].

Timing, dose, and duration of azithromycin for the prophylactic nature of the trial were selected following completion of a systematic review[4]. To our knowledge, no data emerging after trial initiation, suggest that our dose or duration was not optimal. We would be pleased to see publication of the data from Thomas et al. supporting their proposed treatment regime for preterm-born infants still requiring ventilation beyond six weeks of age, but these infants are very different from infants we recruited after requiring respiratory support within 72 hours of birth; only few of these infants remained

ventilated at 6 weeks of age. We advocate the considered approach that we followed with coherent development of the elements of randomised trials including dosage, validated assessments that are known to be consistently deployed across multiple centres, and phenotypes used for stratification or post hoc analysis that are identified before trials are opened. This approach takes time but are likely to lead to robust results.

References:

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