# Single Dose Antenatal Corticosteroids (SNACS) Non-Inferiority Randomized Control Trial for Women at Risk of Preterm Birth

**RATIONALE:** *In utero* exposure to antenatal corticosteroids (ACS) decreases neonatal mortality and morbidity in infants who are born preterm, as summarized in a recent Cochrane review of 30 trials using similar doses--but **are we giving too high a dose?** ACS deliver a **stress signal** to the fetus, forcing early organ maturation, which in the lungs, increases: surfactant, lung compliance and fluid reabsorption.

ACS were first trialed for enhancement of fetal lung maturation in 1972. During the intervening almost **half a century**, **identical or nearly identical standard ‘double dose’ have been used**. *However, a fundamental “guiding principle of therapeutics is to use the lowest effective dose”.* Thus, *it is “astonishing*” that although ACS have been used for nearly 50 years, *the dose of ACS remains virtually unstudied in humans,* despite concerns about potential toxicity.  **Adverse effects with standard ‘double dose’ ACS** have been clearly documented in animals, ranging from reduction of hippocampal neurons to reduction of glomeruli. Moreover, ACS alteration of DNA methylation persists as far out as the *third generation* (i.e. the ‘grandchildren’ of exposed female and male animals). In human infants who are born preterm, recent evidence after a standard double dose of ACS suggests higher rates of allergies, higher insulin levels, cardiovascular impacts (higher systolic blood pressures44, decreased heart rate variability45, and decreased aortic distensibility) and decreased adult kidney function. Infants born at term after a double dose have increased neurosensory adverse outcomes and higher chance of being in the lower quartile of performance at school. Animal research suggests that **half the current dose** is equally effective at maturing preterm lungs, and now a trial is urgently required in humans.

**RESEARCH QUESTION:** For women at 220/7-336/7 weeks of gestation who are at risk of preterm birth, compared to a *standard* double dose of 12 mg betamethasone 24 hours apart, is an *experimental* single 12 mg betamethasone dose followed by placebo, 24 hours apart, *non-inferior* at a margin of ? 70% in the prevention of a composite outcome of neonatal mortality or significant neonatal morbidity? (Significant neonatal morbidity is defined as: **1**) early respiratory morbidity defined as either a) requiring surfactant < 3 days of life or b) need for mechanical ventilation < 3 days of life, OR **2**) late respiratory morbidity, defined as bronchopulmonary dysplasia i.e. requiring oxygen at a postnatal gestational age of 36 completed weeks OR **3**) severe intraventricular hemorrhage (grade III, distending the cerebral ventricles or IV, beyond the ventricles) OR **4**) necrotizing enterocolitis defined as either perforation of intestine, pneumatosis intestinalis or air in the portal vein.)

Among *other secondary*outcomes: neurodevelopmental and behavioural outcomes at 18-24 months and anthropometry at birth and 18-24 months.

**DESIGN**: This is a multicentre, triple blind, pragmatic, noninferiority RCT, with stratification for gestational age at randomization (220/7-276/7 vs 280/7-336/7 weeks) and centre.

**Inclusion criteria:** Pregnant women capable of giving consent, with a singleton, twin or triplet gestation between > 220/7 and < 336/7 weeks’ gestation who have been given the first dose of 12 mg betamethasone as they are deemed by their physician to be at risk of preterm birth will then be randomized to receive within 24 hours either:1) 12 mg of betamethasone (control arm), or 2) equal volume, similar appearing placebo (experimental arm).

The final **analysis** will be based on both an “intention to treat” approach and a ‘per protocol’ approach. **Planned subgroups** include: Gestational age categories 22-28, 29-33, 34-36and >37 weeks; birth < 7 days of intervention, female vs male and multiple gestations.

Our **team** involves parents, obstetricians, neonatologists, statisticians, developmental follow-up pediatricians experienced at clinical trials.

**Clinical impact**: If a single dose of ACS is found to be non-inferior to standard double doses, this trial will not only improve our understanding of ACS, decrease potential toxicities, decrease costs, but potentially contribute to informed decision-making with patients, apprise clinical practice guidelines and will have the potential to change practice patterns nationally and internationally.

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