

WORLD HEALTH ORGANIZATION

Department of Sexual, reproductive, maternal, Child and Adolescent Health and Ageing

TRIAL PROTOCOL

Implementation Research to Scale-up and Evaluate the Impact of Antenatal Corticosteroids and small/sick newborn care on Preterm Newborn Outcomes in Bangladesh, Ethiopia, Nigeria and Pakistan

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TRIAL SUMMARY

Title Implementation Research to Scale-up and Evaluate the Impact of Antenatal Corticosteroids and small/sick newborn care on Preterm Newborn Outcomes

Aim To evaluate the impact of an optimized implementation model, combining safe antenatal corticosteroid (ACS) use, strengthened intrapartum care, and small and sick newborn care (SSNC), on mortality (stillbirth or neonatal death up to 28 days) among preterm births.

Design Two-arm, parallel cluster-randomised controlled trial (cRCT) with a standardisation phase, baseline phase, transition phase, and 12-month intervention period.

Setting Thirty-two networks of care (clusters) across four countries (eight per country), each comprising one or more core CEmONC facility and associated peripheral facilities.

Population: Health workers are direct participants receiving the intervention. Women and newborns are recipients of care and contribute outcome data through routine clinical documentation.

Intervention: Optimized ACS implementation model including safe ACS use, strengthened intrapartum care, and SSNC across eight domains. Specific interventions across these three areas include mentorship, training of health workers (HW), creation of clinical champions, provision of clinical protocols & job aids, audit and feedback mechanisms, referral strengthening, and community engagement including Information, Education, and Communication (IEC) materials.

Control: Usual care with dissemination of WHO recommendations.

Primary Outcome: Any baby death (stillbirth or neonatal death up to 28 days) among preterm newborns (≥ 28 to < 37 weeks gestation or birthweight ≥ 1000 – 2000 g).

Secondary Outcomes: Neonatal mortality, stillbirth rate, ACS coverage and ACS (Judgement of imminence), maternal postpartum infection, SSNC indicators (CPAP, KMC, breastfeeding, hypothermia, implementation outcomes & cost-effectiveness).

Sample Size: Estimated 100–169 preterm births per cluster per month across 32 clusters, providing $\geq 90\%$ power to detect a 25% relative reduction in the primary outcome.

Duration: Twenty-one months per cluster (6-month baseline, 3-month transition, 12-month intervention).

1. ADMINISTRATIVE INFORMATION

1.1 Title

This protocol, titled *Implementation Research to Scale-up and Evaluate the Impact of Antenatal Corticosteroids and small/sick newborn care on Preterm Newborn Outcomes*, outlines the design and implementation of a multicounty evaluation of an optimized model to improve preterm birth outcomes in Bangladesh, Ethiopia, Nigeria and Pakistan. It describes the scientific rationale, methodology, operational arrangements, and ethical considerations for conducting the trial across four countries.

1.2 Trial Registration

The trial has been registered in a WHO-recognised primary clinical trials registry prior to enrolment. (ISRCTN15483467)

1.3 Protocol Version

This document represents Protocol Version 1.7, dated 15-08-2026. Any subsequent amendments will be documented, dated, and submitted to relevant ethics committees and regulatory authorities in accordance with WHO procedures.

1.4 Funding

The trial is funded by the Bill & Melinda Gates Foundation under Grant INV-005390_2020. Funding covers study design, implementation, data collection, monitoring, analysis, and dissemination activities across all participating countries. The sponsor, the World Health Organization, retains full responsibility for scientific oversight, protocol governance, and ethical compliance.

1.5 Roles and Responsibilities

The World Health Organization (WHO) serves as the sponsor and provides overall leadership for the trial. The WHO Trial Coordinating Unit, based in Geneva, is responsible for protocol oversight, coordination across countries, regulatory compliance, and harmonisation of procedures. Country Principal Investigators in Bangladesh, Ethiopia, Nigeria, and Pakistan oversee national implementation, secure ethical and administrative approvals, and coordinate with Ministries of Health and participating facilities.

An independent Trial Steering Committee provides scientific oversight; reviews progress and ensures adherence to protocol standards. An independent Data Safety Monitoring Committee (DSMC) monitors participant safety, reviews interim data, and advises on continuation, modification, or termination of the trial. Local research teams in each country manage day-to-day implementation, including training, data collection, quality assurance, and coordination with networks of care.

The trial receives ethical oversight from the WHO Ethical Review Committee (ERC) and national Ethical Review boards in the participating countries.

2. INTRODUCTION

2.1 Background and Rationale

Preterm birth remains one of the leading causes of neonatal mortality worldwide, with the highest burden concentrated in low-resource settings where access to high-quality maternal and newborn care is limited. Antenatal corticosteroids (ACS) are a proven intervention for improving outcomes among women at risk of preterm birth, but their safe and effective use requires specific clinical and

system-level conditions¹. Evidence from the WHO-coordinated ACTION-I trial^{2, 3} demonstrated that ACS can substantially reduce neonatal mortality in early preterm births when administered under conditions aligned with WHO guidance. These conditions include accurate gestational age assessment, identification of imminent preterm birth, absence of maternal infection, adequate childbirth care, and availability of essential preterm newborn care.

In contrast, the earlier ACT trial⁴ highlighted potential harms associated with scaling ACS use in settings where these conditions were not met. Increased maternal infection and neonatal mortality were observed when ACS was administered without adequate diagnostic capacity, referral systems, or newborn care. Together, these findings underscore the need for a carefully designed implementation strategy that ensures ACS is used safely and appropriately in low-resource settings.

To address this need, formative research (phase 1) was conducted in Bangladesh, Ethiopia, Nigeria, and Pakistan to identify barriers and facilitators to safe ACS use. An initial implementation model was developed and iteratively refined through program learning until high coverage of safe ACS use was achieved across sites. The optimized implementation model integrates three components: safe ACS use, strengthened intrapartum care, and small and sick newborn care (SSNC). This model was designed to ensure that ACS is administered only when clinically appropriate and that preterm newborns at risk of complications receive timely, high-quality care.

Phase 2 of this multicounty study will evaluate the impact of scaling up the optimized implementation model on preterm mortality across networks of care. The evaluation will be conducted through a two-arm, parallel cluster-randomised trial with a baseline phase, allowing robust assessment of mortality outcomes and implementation fidelity in routine health system settings. The trial will also generate evidence on implementation processes, contextual influences, and health system readiness, contributing to global guidance on safe ACS use and preterm newborn care. This protocol describes the Phase 2 cluster-randomised trial.

Rationale for implementation research in low- and middle-income countries (LMICs)

Despite antenatal corticosteroids (ACS) being a standard of care in high-income countries, with coverage exceeding 90%⁵, use remains substantially lower and inconsistent across low- and middle-income countries (LMICs). Across 75 Countdown countries, ACS coverage in secondary and tertiary hospitals is estimated at 41%⁶. In the WHO Multi-Country Survey on Maternal and

¹ Vogel JP, Oladapo OT, Pileggi-Castro C, Adejuyigbe EA, Althabe F, Ariff S, et al. Antenatal corticosteroids for women at risk of imminent preterm birth in low-resource countries: the case for equipoise and the need for efficacy trials. *BMJ Glob Health*. 2017 Aug;2(3):e000398.

² WHO ACTION Trials Collaborators. Antenatal dexamethasone for early preterm birth in low-resource countries. *N Engl J Med*. 2020 Dec 24;383(26):2514-2525. doi: 10.1056/NEJMoa2022398.

³ WHO ACTION Trials Collaborators. The World Health Organization ACTION-I (Antenatal Corticosteroids for Improving Outcomes in preterm Newborns) Trial: a multi-country, multi-centre, two-arm, parallel, double-blind, placebo-controlled, individually randomized trial of antenatal corticosteroids for women at risk of imminent birth in the early preterm period in hospitals in low-resource countries. *Trials*. 2019;20(1):507.

⁴ Althabe F, Belizan JM, McClure EM, Hemingway-Foday J, Berrueta M, Mazzoni A, et al. A population-based, multifaceted strategy to implement antenatal corticosteroid treatment versus standard care for the reduction of neonatal mortality due to preterm birth in low-income and middle-income countries: the ACT cluster-randomised trial. *Lancet*. 2015;385(9968):629-39

⁵ Lawn JE, Segre J, Barker P, Smith J, De La Torre I, Stones W. Antenatal corticosteroids to reduce preterm deaths in low-income settings. *Lancet Glob Health*. 2014 Aug;2(8):e446.

⁶ Bhutta ZA, Das JK, Bahl R, Lawn JE, Salam RA, Paul VK, et al. Lancet Newborn Interventions Review Group; Lancet Every Newborn Study Group. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? *Lancet*. 2014;384(9940):347-70

Newborn Health, ACS use ranged from 16% to 75% even in high-volume referral facilities, with uncertainty regarding whether administration met safety criteria⁷.

The ACTION-I Trial, the largest placebo-controlled evaluation of ACS to date, demonstrated that ACS can reduce neonatal mortality when used under appropriate conditions. However, safe translation of these findings into LMIC practice requires adherence to the five WHO-recommended⁸ criteria for ACS administration: (1) accurate gestational age assessment; (2) imminent risk of preterm birth; (3) absence of maternal infection; (4) availability of adequate childbirth care; and (5) capacity to provide essential preterm newborn care, including resuscitation, kangaroo mother care, thermal care, feeding support, infection management, safe oxygen use, and CPAP. These criteria collectively define *safe ACS use* and form the basis of an optimized implementation model.

Current guidance provides limited direction on how LMIC health systems can operationalize these requirements. Key gaps include improving access to reliable gestational age assessment, strengthening identification of women most likely to benefit from ACS, and ensuring facility readiness to provide high-quality childbirth and newborn care—particularly where specialized equipment (e.g., CPAP) is required.

Implementation research is therefore essential to determine how to safely increase coverage of appropriate ACS use while simultaneously improving preterm childbirth and newborn care. It is also necessary to establish whether optimized ACS implementation models, when scaled under real-world LMIC conditions, are safe and lead to reductions in neonatal and perinatal mortality.

We propose a multi-country implementation research study to:

- Identify barriers and enablers to scaling safe ACS use;
- Develop and test programmatic solutions tailored to LMIC contexts;
- Implement optimized ACS models to achieve high coverage of safe ACS use alongside strengthened childbirth and newborn care; and
- Evaluate the population-level impact on neonatal and perinatal outcomes.

Findings, tools, and implementation resources will be disseminated widely to support adoption and scale-up of safe ACS use across LMICs.

2.2 Objectives

Primary Objective

To determine the impact of the optimized implementation model on any baby death—defined as stillbirth or neonatal death up to 28 days of life—among preterm newborns (≥ 28 to < 37 weeks gestation by earliest ultrasound else, in the absence of a ultrasound, birthweight ≥ 1000 – 2000 g).

⁷ Vogel JP, Souza JP, Gulmezoglu AM, Mori R, Lumbiganon P, Qureshi Z, et al. Use of antenatal corticosteroids and tocolytic drugs in preterm births in 29 countries: an analysis of the WHO Multicountry Survey on Maternal and Newborn Health. *Lancet*. 2014;384(9957):1869-77.

⁸ World Health Organization. WHO recommendations on interventions to improve preterm birth outcomes [Internet]. Geneva, Switzerland: World Health Organization; 2015 [cited 2025 May 20]. 98 p. Available from: <https://iris.who.int/handle/10665/183037>

Secondary Objectives

To evaluate the effect of the optimized implementation model on:

- Neonatal mortality rates among preterm, early preterm, and all births
- Stillbirth rates among preterm and all births
- Coverage of ACS and safe ACS use
- ACS (Judgement of imminence)
- Maternal postpartum infection
- Place of birth and referral patterns for early preterm births
- Coverage of SSNC components in the eight domains of care, including, safe referral, breastfeeding support, CPAP and KMC.
- Implementation outcomes such as fidelity, feasibility, acceptability, adoption, reach, and contextual influences

2.3 Trial Design

This study is a two-arm, parallel cluster-randomised controlled trial (cRCT) with a baseline control phase and a defined transition period. Thirty-two networks of care (clusters) will participate, with eight clusters per country across Bangladesh, Ethiopia, Nigeria, and Pakistan. Clusters will be randomised in a 1:1 ratio to either control or intervention (Figure 1).

Each cluster represents a network of health facilities comprising at least one core facility capable of providing comprehensive emergency obstetric and newborn care (CEmONC) and associated peripheral facilities conducting at least ten births per month.

Standardisation

Standardisation of the outcome measure (identification of preterm birth) - This activity will precede the trial (baseline) in both control and intervention clusters (Figure 8). It will involve increasing access to ultrasound for gestational age dating for all pregnant women either through the provision of ultrasound equipment when necessary and ensuring an increased pool of trained staff and/or increased opening time for accessing services. Besides this the project will provide training in birthweight measurements, and the provision of digital weighing scales will be provided to all participating facilities.

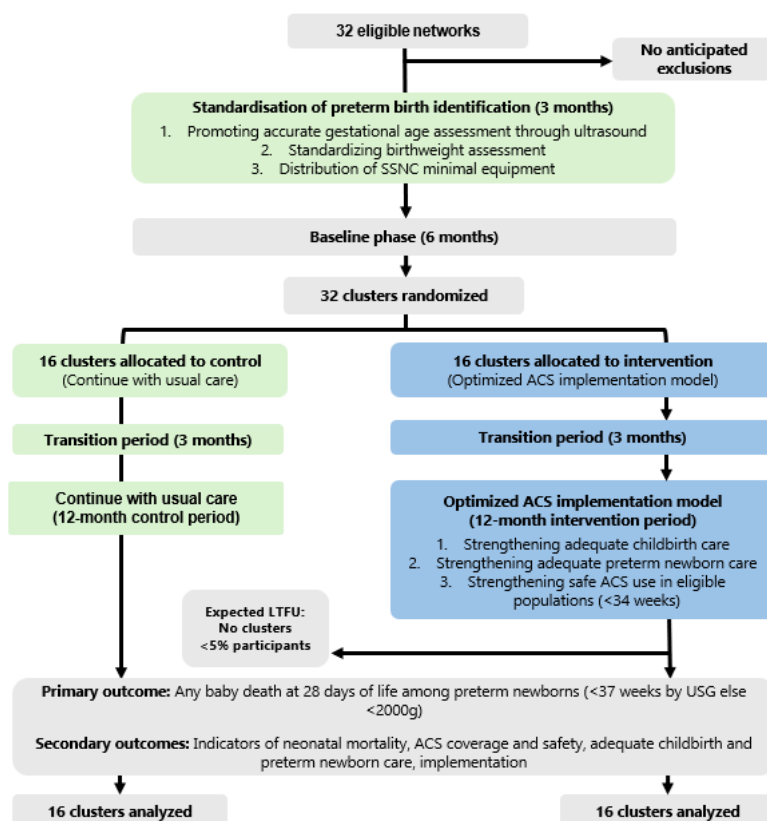
In addition, essential equipment for SSNC care in the labour room and SNCU will be provided across all clusters (CPAP, pulse oximeters, radiant warmers, glucometers).

The trial consists of three sequential phases:

- Baseline phase (6 months): All clusters provide usual care while outcome and process data are collected to establish pre-intervention levels.

- Transition phase (3 months): Following randomisation, intervention clusters receive training, readiness support, and begin embedding the optimized ACS model; control clusters continue usual care. Data from this phase are collected but excluded from primary outcome analysis.
- **Intervention/control condition (Post-Transition):** Intervention clusters implement the optimized model at scale, while control clusters continue usual care. Primary and secondary outcomes are assessed during this period.

Figure 1: SPIRIT Flow Diagram



Justification

A cluster-randomised design is required because the intervention is delivered at the health-system and facility-network level. Individual randomisation would be impractical and risk contamination between health workers and facilities. The parallel-with-baseline design improves statistical efficiency and power, given the limited number of clusters and the moderately prevalent outcomes under study.

3. PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

3.1 Study Setting

The trial will be conducted in 32 networks of care across Bangladesh, Ethiopia, Nigeria, and Pakistan. Each network comprises a core facility capable of providing CEmONC and a set of surrounding peripheral facilities conducting at least ten births per month. These networks typically serve 10,000–12,000 births per year, including approximately 1,200 preterm births, and represent

routine health system environments where improvements in ACS use and newborn care could have substantial impact on preterm newborn outcomes.

All participating networks have a high proportion of facility births and baseline safe ACS coverage below 40%, ensuring relevance for evaluating the optimized ACS implementation model. Prior to trial initiation, all networks will undergo a three-month standardisation to strengthen gestational age and birthweight assessment, enabling accurate identification of preterm births for outcome measurement.

3.2 Eligibility Criteria

Cluster

Each cluster (or network) comprises a core facility capable of providing CEmONC and a set of surrounding peripheral facilities conducting at least ten births per month.

Clusters must meet predefined criteria to ensure adequate preterm birth volume, readiness for implementation, and comparability across countries. Eligible clusters:

- Serve approximately 10,000–12,000 births per year
- Include ≥ 300 early preterm births (< 34 weeks) per year at the facility level or $\geq 1,200$ preterm births (< 37 weeks) per year across the network
- Have baseline Safe ACS coverage $< 40\%$ among preterm births < 34 weeks, based on best available information.
- Include at least one CEmONC facility with a Level-2 Special Newborn Care Unit (SNCU) designated as core facility. Include all peripheral (e.g. primary health care) facilities that have > 10 deliveries per month, including from the private sector, where births occur in the geographically-defined health administrative area and refer to the core facilities.

All health workers employed in the network of care (cluster) who provide antenatal, intrapartum, or newborn care will be the focus of study intervention.

All women who give birth in the network of care (≥ 28 weeks gestation by ultrasound or birthweight $\geq 1000\text{g}$) & provide consent for data sharing will be included in the study.

3.3 Interventions

Optimized ACS Implementation Model (Intervention Arm)

Intervention clusters will implement the optimized ACS implementation model, comprising three integrated components:

Safe ACS Use

Safe ACS use requires correct identification of eligible women, appropriate administration of ACS, and ensuring delivery in a facility capable of providing adequate childbirth and newborn care. This includes:

- **Right woman:** Accurate gestational age assessment (< 34 weeks), high likelihood of preterm birth within seven days, and absence of maternal infection
- **Right treatment:** Administration of dexamethasone (6 mg IM every 12 hours $\times$ 4 doses) or betamethasone (12 mg IM every 24 hours $\times$ 2 doses), alongside co-interventions such as

antibiotics for PPROM, tocolytics where indicated, and magnesium sulphate for fetal neuroprotection (<32 weeks)

- **Right place:** Strengthened referral pathways to ensure eligible women can complete ACS dosing and receive adequate childbirth and newborn care

Strengthened Intrapartum Care

Strengthened intrapartum care includes continuous monitoring during preterm labour, use of the WHO Labour Care Guide adapted for preterm labour, timely clinical response, and improved emergency readiness. Core facilities must have 24-hour caesarean section capability, adequate staffing, essential equipment, and reliable documentation systems.

Small and Sick Newborn Care (SSNC)

SSNC includes strengthening eight domains of newborn care:

1. Care at birth (resuscitation, early identification, safe referral)
2. Kangaroo mother care (KMC)
3. Breastfeeding and breastmilk feeding support
4. Infection prevention and IV fluids
5. Respiratory support (CPAP and safe oxygen use)
6. Thermal care and monitoring
7. Management of infection and common conditions
8. Developmentally supportive care

Implementation Strategies

Implementation strategies include:

- 1) Mentorship
- 2) Clinical Champions
- 3) Onsite training
- 4) Clinical protocols & Job Aids
- 5) Audit & feedback
- 6) Community & family engagement and IEC materials.

Table 1. The key components of the Phase 2 optimized ACS implementation model

Component of the ACS Implementation model	Place	Intervention
Right woman (ACS administered to women with high probability of preterm birth within 7 days;	Core facilities	1. Training of Health Workers: Health workers to be trained on the identification and management of women at high risk of preterm birth.
		2. Clinical Protocols: Clinical protocols focusing on the diagnosis and treatment of women at high risk of preterm birth to be disseminated and approved by hospital

ACS administered in women with no clinical signs of infection) Right treatment (administration of 24mg of ACS in divided doses; antibiotics for PPROM; tocolytics if not contraindicated; MgSO4 for neuroprotection in women giving birth <32 weeks) Right place (peripheral facility can identify potentially eligible population for ACS treatment and refer to core facility)		leadership and district-level authorities.
		3. Audit and Feedback Sessions: Monthly audit and feedback meetings to be held to assess progress of safe coverage of ACS in the facility and in the network of care, as well as to monitor any misuse of ACS as well as review all cases of preterm births at <34 weeks' gestation, aiming to identify any gaps or missed opportunities in patient management. A facility-based dashboard to be displayed monthly to facilitate this process together with a network-based dashboard, to follow the overall performance of the network.
		4. Weekly checklists for stock, equipment and human resources Control: weekly checklists compiled to ensure proper forecasting and stock management as well as availability of human resources and functioning of equipment such as ultrasound machines.
		5. Champions: Champions to be nominated in each facility representing both maternal and newborn care to ensure the uptake of the model, leading by example, motivating facility staff, and conducting audit and feedback sessions.
	Peripheral facilities	1. Training of Health Workers: Health workers to be trained on the identification, ACS administration, and referral of women at high risk of preterm birth.
		2. Clinical Protocols: Clinical protocols focusing on the diagnosis and referral of women at high risk of preterm birth to be disseminated and approved by hospital leadership.
Community	1. Briefing of Community Health Workers on Early Ultrasound and Preterm Birth: Community health workers (CHWs) operating within the network of care area to be provided with briefing sessions emphasizing the importance of early ultrasound for accurate pregnancy dating and the identification and referral of women at risk of early preterm birth.	
	2. Development and Dissemination of IEC Materials: Informational, educational, and communication (IEC) materials, including brochures for women and families (in local language), aimed at highlighting the signs and symptoms of preterm birth and the importance of delivering preterm infants in appropriate facilities to be disseminated by CHWs as well as during antenatal care visits.	
Intrapartum care	Network of care	1. Training of Health Workers: Health workers to be trained on the appropriate monitoring of women during preterm labour and birth and strengthen recording practices, including introduction of the WHO labour care guide (LCG) adapted for preterm labor (PTL)/preterm birth (PTB).
Small/sick newborn care	Network of care	1.Mentorship: Mentors will focus on building skills onsite and through online consultations as per need based on observations, audit and feedback meetings and 6 mentors visits.
		2. Clinical Champions: Clinical champions will be trained by mentors in the eight domains of SSNC, take a leadership role in their own facility and facilitate the onsite training of HWs.
		3. Onsite training: A team of Mentors and Champions will train all HWs in the network of care in the eight domains of SSNC applicable to their field.
		4. Clinical protocols & Job aids: Distribute & display tailored job aids on the WHO recommendations for SSNC care in the eight domains.
		5. Audit & feedback meetings (inc. data review). Monthly meetings to facilitate feedback on progress based on data.
		5. Family engagement & IEC materials: Mentor led advocacy from women & families in the SNCU. IEC materials for women and families on KMC, Breastfeeding, Hand hygiene and danger signs distributed and displayed in all facilities.

Control Arm

Control clusters will continue usual care with dissemination of WHO recommendations but with no other implementation support. In addition, they will receive newborn care equipment according to the minimal requirements for delivery of SSNC.

3.4 Outcomes

Definitions

Early Preterm: ≥ 28 to < 34 weeks gestation by earliest ultrasound, else in the absence of a USG Birthweight ≥ 1000 g to ≤ 1500 g

Preterm: ≥ 28 to < 37 weeks gestation by earliest ultrasound, else in the absence of a USG Birthweight ≥ 1000 g to ≤ 2000 g

Term: ≥ 37 weeks gestation by earliest ultrasound, else in the absence of a USG Birthweight > 2000 g

All births: ≥ 28 weeks gestation by earliest ultrasound, else in the absence of a USG Birthweight ≥ 1000 g

Neonatal mortality: Neonatal death up to 28 completed days of life

Any baby death: Stillbirth or neonatal death up to 28 completed days of life

Primary Outcome

Any baby death among preterm newborns, defined as:

- Stillbirth, or
- Neonatal death up to 28 completed days of life

among births at:

- ≥ 28 to < 37 weeks gestation by earliest ultrasound, else
- Birthweight ≥ 1000 g to ≤ 2000 g when gestational age by ultrasound is unavailable.

Secondary Outcomes

Mortality Outcomes

- Any baby death among all early preterm & all births
- Neonatal mortality among liveborn preterm, early preterm, and all births
- Stillbirth among all preterm births and all births

Process Outcomes: Maternal

- **ACS coverage:** Proportion of all liveborn EPTs who receive ACS
- **Safe ACS coverage:** Proportion of all liveborn EPTS who receive ACS and are delivered in a core facility
- **Effective ACS coverage:** Proportion of all liveborn EPTs who received a full course of ACS

- **ACS (Judgement of imminence):** Proportion of all women who receive ACS <34 gestation who deliver at term.
- **Effective Tocolysis:** The proportion of all liveborn EPT births that receive ACS and are born less than 24 hours from dose 1 who received both ACS & tocolysis.
- **LCG use:** Proportion of all preterm births in which the WHO LCG was used
- **Place of birth:** Proportion of all EPTs born at a core facility

Secondary Process Outcomes: Newborn

- **KMC coverage:** Proportion of all preterm newborns who received KMC
- **CPAP coverage:** Proportion of all liveborn EPTs who received CPAP
- **Exclusive breastfeeding at day 28:** Proportion of all liveborn preterm newborns who were exclusively breastfed at day 28 of life.
- **Neonatal Resuscitation:** The proportion of all preterm newborns who are resuscitated with bag and mask at birth.

Secondary Safety Outcomes

- **Maternal postpartum infection:** Proportion of all women who have a postpartum infection up to 28 completed days after birth
- **Term neonatal mortality**

Implementation Outcomes

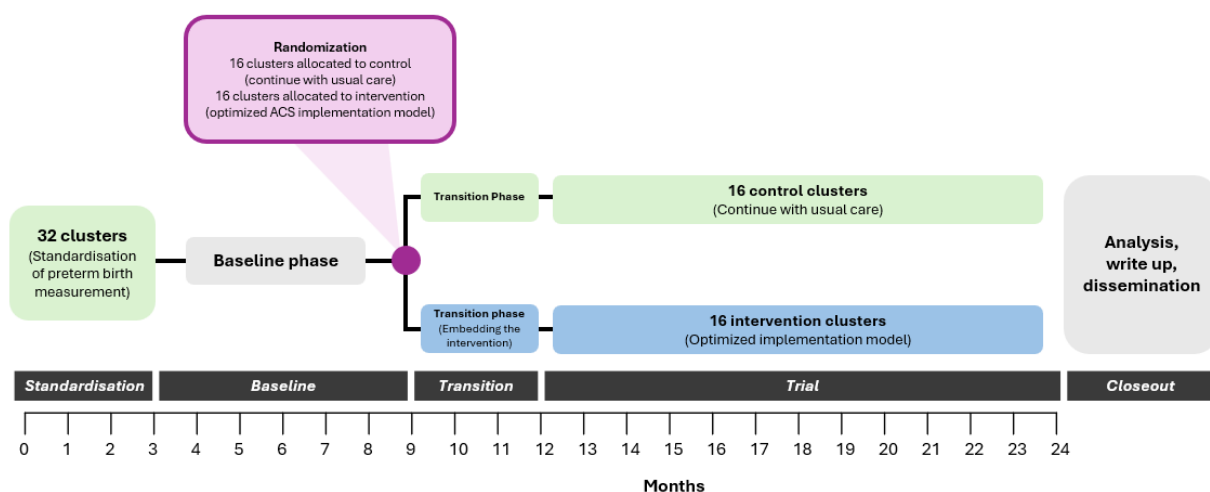
- Implementation outcomes (adoption, fidelity, acceptability, reach, feasibility)

Full outcome definitions are provided in Appendix A.

3.5 Trial Timeline

The trial includes three sequential phases: baseline, transition, and post-transition. Women and newborns contribute data at the time of birth and through routine follow-up to twenty-eight days of life. (Appendix B)

Figure 2: Trial Timeline



3.6 Sample Size

The sample size is based on detecting a twenty-five percent relative reduction in the primary outcome. With thirty-two clusters and an estimated ninety-seven thousand preterm births across the intervention period, the trial has at least ninety percent power to detect the anticipated effect size.

Anticipated cluster sizes were estimated from survey data collected. These estimations are outlined in Table 7 (below).

Table 7. Estimates of average cluster size from preliminary survey data

	Nigeria	Bangladesh	Pakistan	Ethiopia	Combined
Total annual preterm births	9137	22796	14660	17819	64412
Number of clusters	8	8	8	8	32
Average annual preterm births per cluster	1142	2845	1832	2227	2013
Average preterm births per cluster per month	95	238	153	186	168
Coefficient of variation for cluster size	0.23	0.29	0.19	0.31	0.42

Target effect size: We aim to detect a 25% reduction in the relative risk (of any baby death (still birth + neonatal death) among preterm newborns.

Power calculations: Power calculations were performed using an RShiny app for cluster trials (6). All calculations allow for the cRCT design (using the intra-cluster correlation coefficient [ICC]); variations in clustering over time (using the cluster-auto correlation [CAC]); and allow for 5% attrition of individuals. We assume a significance level of 5%.

For the primary outcome of preterm any baby death, we assume a baseline prevalence of 14.1%. Previous studies suggest the ICC for this trial will be in the range of 0.001 to 0.03. There were limited sources for CAC values, and so we follow the practice of assuming a value of 0.80 in our calculations.

For the estimated 25% reduction in preterm perinatal mortality from 14.1% to 10.6%, with a CAC of 0.8 the sample size allows us a power of between 99-90% for an ICC ranging from 0.001 to 0.03.

To test the robustness of the design to variation in the number of preterm births per month a sensitivity analysis was conducted (Appendix C).

3.7 Recruitment

Recruitment occurs at the cluster level. Women and newborns provide consent for individual level data sharing, health workers are not individually recruited.

4. ASSIGNMENT OF INTERVENTIONS

4.1 Allocation

Randomisation will be conducted at the cluster level using a covariate-constrained randomisation algorithm. The allocation sequence will be generated by an independent statistician and stratified by country. The algorithm will balance clusters on baseline values of the primary outcome and cluster size. Randomisation will occur during the baseline phase.

The WHO Trial Coordinating Unit will communicate assignments to country teams at the time of randomisation. Site teams will disclose cluster allocation no earlier than 8 weeks prior to transition. This is to allow essential government level approvals for intervention activities to be obtained and activities to be organised in advance of transition.

4.2 Blinding

Blinding of health workers and facility staff is not feasible due to the nature of the intervention. Outcome assessors and data analysts will be blinded to cluster allocation where possible. Mortality outcomes are derived from routine clinical documentation, reducing risk of differential measurement. Unblinding of outcome assessors may occur only if essential for data verification or safety review, as determined by the DSMC.

5. DATA COLLECTION, MANAGEMENT, AND ANALYSIS

5.1 Data Collection Methods

Data collection will occur across the three trial phases, Baseline, Transition and Post-Transition Phase.

Data on total births, preterm births, stillbirths, neonatal deaths, ACS administration, intrapartum care practices, SSNC indicators (e.g. CPAP, KMC, Breastfeeding,) will be collected across all time periods.

In addition, data on implementation activities will be collected in intervention clusters:

- Transition phase: Data on training completion, distribution of intervention materials (job aids & IEC materials), enrolment of clinical champions, and mentoring visits. This data will be excluded from the primary analysis and used for the process evaluation.

Data sources include maternity registers, labour ward registers, newborn unit registers, referral logs, discharge summaries, day-29 follow-up forms, facility dashboards, and weekly stock and equipment checklists. Data collectors will be trained in standardised procedures and enter the data into facility-based study registers.

Data quality will be promoted using standardised Case Report Forms (CRFs). The trial will employ four CRFs, the Birth & Delivery (BDF) Form, ACS Form, Maternal & Neonatal Follow-up (MNFU) Form & SSNC Form. Research assistants will be trained in the completion of these forms and monthly audit and feedback reviews of data quality. All data entered the electronic data capture system will be checked against validation rules.

5.2 Data Management

All data will be entered into a secure electronic database which will include role-based access control, encrypted storage, audit trails, automatic validation checks, and daily backups. Paper-based source documents will be stored securely at facilities.

Personal identifiers will be removed from analytical datasets. Unique study IDs will be used for women and newborns. Identifiable information will be stored separately from outcome data. Access will be restricted to authorised personnel. Data quality will be monitored through routine audits, cross-checking, and review of missing or inconsistent data. All trial data will be archived according to national regulations.

5.3 Statistical Methods

The primary analysis will compare the risk of any baby death among preterm newborns between intervention and control clusters during the intervention period using mixed-effects logistic regression models. Analyses will adjust for baseline outcome levels, country, cluster size, and clustering. Effects will be expressed as risk ratios, risk differences, and 95% confidence intervals.

Secondary outcomes will be analysed using similar mixed-effects models appropriate to outcome type. Additional analyses will include subgroup analyses (country, place of birth), sensitivity analyses (e.g., excluding clusters with incomplete baseline data, gestational age assessment by birthweight), and per-protocol analyses (clusters with high fidelity). The primary analysis population includes all eligible preterm births in participating clusters during the intervention period. Missing data will be addressed through multiple imputation and sensitivity analyses.

6. MONITORING

6.1 Data Monitoring

An independent DSMC will oversee participant safety, monitor trial conduct. The DSMC will consist of experts in maternal and newborn health, biostatistics, epidemiology, and ethics. It will operate under a formal charter.

The DSMC will review safety outcomes, sample size assumptions, data completeness, data quality, adherence to protocol and protocol deviations. Statisticians blinded to allocation will produce and share summary tables as requested by the DSMC.

6.2 Harms

Because the intervention evaluated in this trial reflects clinical care consistent with WHO recommendations, no adverse events are anticipated as unique or unexpected consequences of trial participation. Expedited reporting of individual adverse events is therefore not proposed.

Adverse maternal and neonatal outcomes, including stillbirths and neonatal deaths, are expected during the trial. Most are likely to reflect the underlying risks of preterm birth and complications of pregnancy and childbirth, rather than the trial intervention.

Nevertheless, key maternal and neonatal outcomes, including stillbirths, neonatal deaths and selected markers of severe neonatal morbidity, will be systematically collected for all eligible participants and reviewed regularly by the independent Data Safety Monitoring Committee (DSMC).

The DSMC will assess overall safety and harm and determine whether any modifications to trial conduct are warranted.

6.3 Auditing

Facility leads will permit trial-related monitoring, audits, inspections, and ethics committee reviews, in line with applicable regulations. Investigators will cooperate and support required follow-up. Where possible, the TCU will be informed in advance of external audits or inspections at country offices or participating facilities.

7. ETHICS AND DISSEMINATION

7.1 Research Ethics Approval

This cluster randomised trial will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP), national regulations, and institutional policies. Ethical approval will be obtained from the WHO Ethics Review Committee (ERC) and all country ethical review boards prior to initiation. Approval will cover the protocol, consent materials for health worker participants, data collection tools, and all participant-facing documents. Cluster-level permission will also be obtained from facility leadership and district health authorities before randomisation and intervention rollout.

7.2 Protocol Amendments

Any protocol amendments that may affect health worker participation, intervention delivery, data collection, or participant safety will be submitted to the ERC for review and approval before implementation. Amendments will be communicated to trial registries, collaborating institutions, and all participating clusters. Updated versions will be circulated to investigators and facility focal persons with clear documentation of changes.

In addition the TCU will conduct Quality Control (QC) routine checks of data completeness and accuracy, consistency between source documents and electronic records, adherence to SOPs, timeliness of data submission. Quarterly QA/QC reports will be produced and reviewed by WHO.

7.3 Consent

Cluster-level permission

Because the intervention modifies facility-level standards of care, permission to conduct the trial will first be obtained from facility leadership and district health authorities. This permission covers randomisation, staff training, and implementation of the updated standard of care at the cluster level.

Health workers: Participation in interviews, focus groups, surveys, and in-depth interviews is voluntary. The study purpose, procedures, and the right to decline or withdraw without consequences will be explained. Written informed consent will be obtained; for those unable to read or write, consent will be read aloud with an impartial witness and documented per local requirements. Confidentiality will be maintained. WHO-approved ICFs will be used.

Pregnant women and newborns: The optimized ACS model and strengthened childbirth/newborn care will be delivered as routine clinical care. Women who decline research participation will continue to receive standard services.

All women admitted for delivery will receive study information and provide **verbal consent** for use of routine maternal and newborn data. Women receiving ACS will provide **written consent** for ACS-specific data collection and newborn follow-up to 29 days. Parents/caregivers will provide **verbal consent** for newborn follow-up. Participation is voluntary, refusal will not affect care, and confidentiality will be ensured according to protocol.

7.4 Confidentiality

All data relating to pregnant women, and newborns will be handled with strict confidentiality. Clinical data for pregnant women and newborns will be extracted from routine records into study registers using anonymised identifiers. All datasets will be stored in password-protected, access-restricted systems. Only authorised study personnel will have access to identifiable information. Data shared with external collaborators will be fully de-identified.

7.5 Declaration of Interests

All investigators will declare any financial or professional conflicts of interest prior to study initiation. No member of the research team will receive personal financial benefit from the intervention or its implementation. Funding sources will be transparently reported in the protocol and all dissemination materials.

7.6 Protecting Vulnerable Participants (Pregnant Women and Newborns)

Pregnant women and newborns are recognised as vulnerable populations. Although they are not enrolled as research participants, they are recipients of an updated standard of care in intervention clusters. The trial incorporates enhanced safeguards to ensure their rights, safety, and wellbeing.

The updated standard of care will be limited to evidence-based, minimal-risk practices aligned with the WHO recommendations. Health workers will receive training on respectful maternity and newborn care, communication with families, and safeguarding principles. Pregnant women will be informed that refusal of data collection does not affect access to care.

These protections ensure that vulnerable recipients of care are safeguarded while allowing evaluation of a cluster-level improvements in standard practice.

7.7 Access to Data and Dissemination Policy

The principal investigators and designated members of the research team will have access to the final dataset. Results will be disseminated through peer-reviewed publications, conference presentations, policy briefs, and stakeholder meetings. Findings will also be shared with participating facilities and district health authorities. No identifiable information about health workers, pregnant women, or newborns will be included in dissemination materials.

Authorship will follow ICMJE criteria. There are no publication restrictions imposed by funders. Trial results will be reported in accordance with CONSORT guidelines for cluster randomised trials.

7.8 Post-Trial Care

The intervention represents an updated standard of care and poses minimal risk. No specialised post-trial clinical follow-up is required for pregnant women or newborns. If the intervention demonstrates benefit, the intervention will be offered to control clusters after trial completion.

7.9 Trial Registration

The trial is registered with a WHO-recognised registry, ISRCTN15483467, prior to enrolment of health worker participants and before implementation of the updated standard of care. Registration will include the protocol, ethics approval details, and a summary of the intervention.

7.10 Publication and Dissemination Policy

Results will be disseminated through peer-reviewed publications, WHO technical reports, presentations at international conferences, policy briefs, and stakeholder workshops. Authorship will follow ICMJE guidelines. WHO will lead manuscript preparation, with contributions from country investigators. The funder will not influence publication decisions.

APPENDICES

Appendix A: Outcome Definitions

Category	Outcome	Population	Definition	Numerator	Denominator
Primary Outcome	Any Baby Death	Preterm	Proportion of all preterm births that are stillbirths or neonatal deaths ≤ 28 days of life	Number of preterm stillbirths or neonatal deaths ≤ 28 days of life	All preterm ^b births (live births + stillbirths)
Secondary Mortality	Any Baby Death	Early Preterm	Proportion of all EPT births that are stillbirths or neonatal deaths ≤ 28 days of life	Number of EPT stillbirths or neonatal deaths ≤ 28 days of life	All early preterm ^a births (live births + stillbirths)
		All Births	Proportion of all births that are stillbirths or neonatal death ≤ 28 days of life	Number of stillbirths or neonatal deaths ≤ 28 days of life	All births ^c (live births + stillbirths)
	Neonatal mortality	Preterm	Proportion of all liveborn preterm births that result in a neonatal death ≤ 28 days of life)	Number of preterm neonatal deaths ≤ 28 days of life	All liveborn preterm ^b births
		Early Preterm	Proportion of all liveborn EPT births that result in a neonatal death ≤ 28 days 28 days of life)	Number of EPT neonatal deaths ≤ 28 days of life	All liveborn early preterm ^a births
		All Births	Proportion of all liveborn births that result in a neonatal death ≤ 28 days 28 days of life)	Number of neonatal deaths ≤ 28 days of life	All liveborn births ^c
	Stillbirth Rate	Preterm	Proportion of all preterm births that are stillbirths	Number of preterm stillbirths	All preterm ^b births (livebirths + stillbirths)
		All births	Proportion of all births that are stillbirths	Number of stillbirths	All births ^c (live births + stillbirths)
Secondary Safety Outcomes	Maternal Postpartum Infection	All Births	Proportion of all women who are readmitted to hospital for a suspected postpartum	Number of women readmitted ≤ 28 days postpartum for suspected infection	All women who had a livebirth

Category	Outcome	Population	Definition	Numerator	Denominator
			infection ≤ 28 days postpartum		
	Neonatal mortality	Term	Proportion of all liveborn term births that result in a neonatal death ≤ 28 days of life)	Number of term neonatal deaths ≤ 28 days of life	All liveborn term ^d births
Secondary Process Outcomes	ACS Coverage	Early Preterm	Proportion of all liveborn EPT newborns who received antenatal corticosteroids (ACS)	Number of liveborn EPT newborns who received ACS	All liveborn early preterm ^a births
	Safe ACS Coverage	Early Preterm	Proportion of all liveborn EPT newborns who received ACS and were delivered in a core facility	Number of liveborn EPT newborns who received ACS and were delivered in a core facility	All liveborn early preterm ^a births
	ACS (judgement of imminence)	Women who receive ACS < 34 weeks gestation	Proportion of women who receive ACS < 34 weeks by USG who deliver ≥ 37 weeks	Number of women receiving ACS < 34 weeks by USG who deliver ≥ 37 weeks	All women who receive ACS < 34 weeks gestation by USG
	Effective ACS coverage	Early Preterm	Proportion of all liveborn EPTs who received a full course of ACS	Number of liveborn EPTs who received a full course of ACS	All liveborn early preterm ^a births
	Effective Tocolysis	Early Preterm	Proportion of all liveborn EPTs who received ACS & tocolytics among all liveborn EPTs who received ACS and delivered < 24 hours from the first dose of ACS	Number of liveborn EPTs who received ACS & tocolytics and were born < 24 hours from ACS dose 1	All liveborn early preterm births who received ACS and were born < 24 hours from ACS dose 1.
	LCG use	Preterm	Proportion of all preterm births where the WHO LCG was used	Number of preterm births where WHO LCG was used	All preterm ^b births (live births + stillbirths)

Category	Outcome	Population	Definition	Numerator	Denominator
	Place of birth	Early Preterm	Proportion of all early preterm births at a core facility	Number of early preterm births at a core facility	Number of early preterm births
	KMC	Preterm	Proportion of preterm newborns receiving any kangaroo mother care (KMC) ≤28 days of life	Number of preterm newborns receiving any KMC in first 28 days of life	All preterm ^b newborns alive at 28 day follow-up
	CPAP	Early Preterm	Proportion of all early preterm newborns who received any CPAP	Number of all early preterm newborns who received any CPAP	All liveborn early preterm ^a births
	Breastfeeding	Preterm	Proportion of preterm newborns exclusively breastfed at day 28 of life	Number of preterm newborns exclusively breastfed at day 28	All preterm ^b newborns alive at 28 day follow-up
	Neonatal Resuscitation	Preterm	Proportion of all preterm births who receive bag and mask resuscitation	Number of preterm resuscitated with bag and mask	All preterm newborns
Process Indicators	USG Coverage	All births	Proportion of births with gestational age assessed by ultrasound	Number of births with gestational age assessed by ultrasound	All births ^c (live births + stillbirths)
	Timing of USG	All births	Proportion of women who had their earliest ultrasound before 24 weeks gestation	Number of women with earliest USG conducted before 24 weeks gestation	All women delivering ≥28 weeks gestation ^c
	Mode of Delivery	Preterm	Proportion of preterm births delivered by cesarean section	Number of preterm births delivered by cesarean section	All preterm ^b births (live births + stillbirths)
		Population definitions: ^a Early Preterm (EPT): born ≥28 to <34 weeks gestation by earliest USG; else ≥1000 g to ≤1500 g in the absence of USG. ^b Preterm: born ≥28 to <37 weeks gestation by earliest USG; else ≥1000 g to ≤2000 g in the absence of USG. ^c All births: born ≥28 weeks gestation by earliest USG; else ≥1000 g in the absence of USG. ^d Term: born ≥37 weeks gestation by earliest USG; else >2000 g in the absence of USG. *			

Category	Outcome	Population	Definition	Numerator	Denominator
		SPIRIT 2025 item 16: <i>For each outcome, the specific variable and analysis metric (proportion or rate per 1000) are included in the Definition column; the time point is embedded in the Numerator or Denominator column as appropriate.</i>			

Appendix B: Abbreviations

ABBREVIATIONS	
Abbreviation	Term
ACS	Antenatal corticosteroids
ACS-IR	Antenatal corticosteroids implementation research
ACTION-I	Antenatal Corticosteroids for Improving Outcomes in Preterm Newborns
CEmONC	Comprehensive emergency obstetric and newborn care
CI	Chief Investigator
CPAP	Continuous positive airway pressure
CRF	Case Report Form
cRCT	Cluster randomised Control Trial
CIOMS	Council for International Organisation of Medical Science
DSMC	Data Safety Monitoring Committee
NEML	National Essential Medicine List
GA	Gestational age
GDPR	General Data Protection Regulation
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
ISF	Investigator Site File
KMC	Kangaroo mother care
LMIC	Low- and Middle-Income Countries
NPI	National Principal Investigator
PIS	Participant Information Sheet
REC	Research Ethics Committee
TCU	Trial Coordinating Unit
TSC	Trial Steering Committee
USG	Ultrasound Sonography
WHO	World Health Organization
WMA	World Medical Association

Appendix C: Sensitivity analysis

Sensitivity Analysis: estimation of study power under lower target recruitment

Cluster size assumptions are based on pre-trial survey data, estimating roughly 1,014 preterm births per cluster-period (equating to approximately 169 per month per cluster). To examine the robustness of the design against smaller cluster sizes, additional sensitivity analyses were conducted (Figure S1 & S2). The figures illustrate power by cluster size per period (where a period is 6 months). Where a cluster size of greater than 67 preterm per cluster per month (400 per 6-month cluster period) is sufficient to maintain power under the given scenarios.

Figure S1: Estimation of power as a function of cluster size per 6-month period (CAC = 0.6)

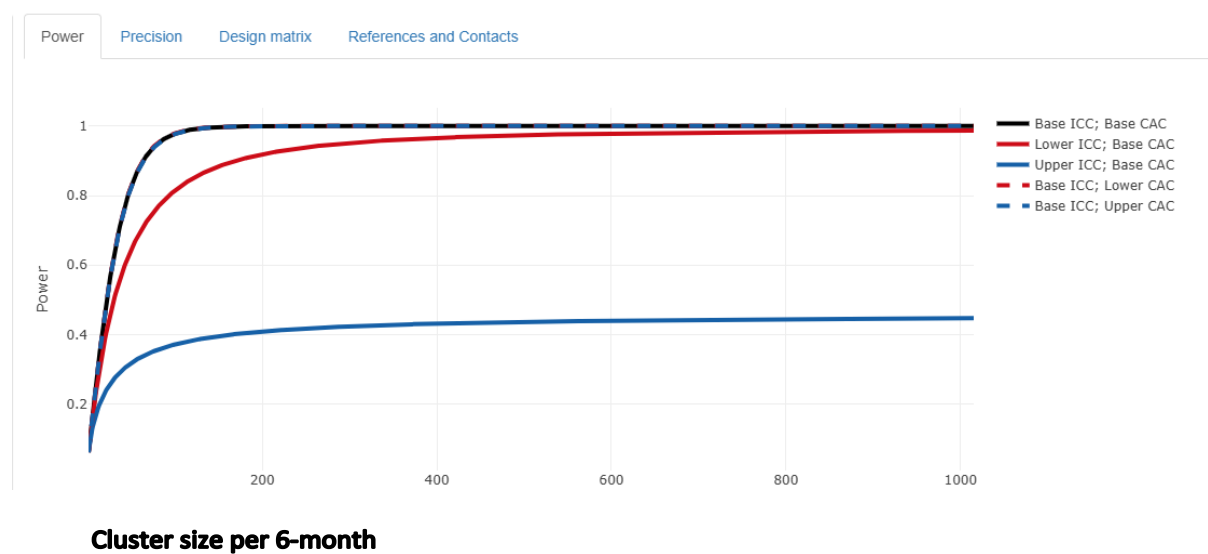
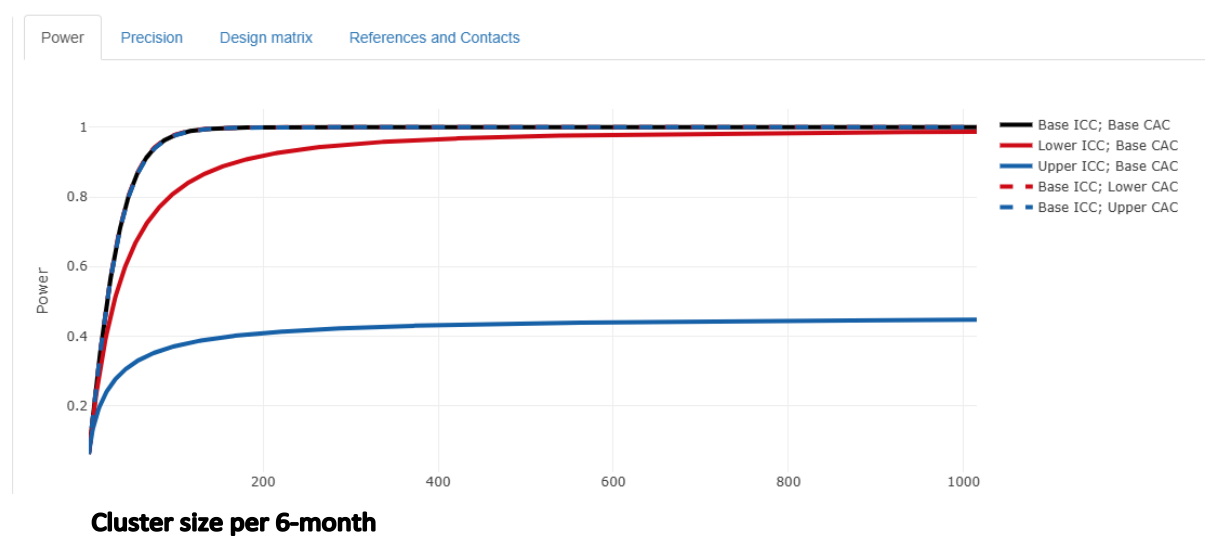


Figure S2: Estimation of power as a function of cluster size per 6-month period (CAC = 0.8)



References

1. Vogel JP, Oladapo OT, Pileggi-Castro C, Adejuyigbe EA, Althabe F, Ariff S, et al. Antenatal corticosteroids for women at risk of imminent preterm birth in low-resource countries: the case for equipoise and the need for efficacy trials. *BMJ Glob Health*. 2017 Aug;2(3):e000398.
2. WHO ACTION Trials Collaborators. Antenatal dexamethasone for early preterm birth in low-resource countries. *N Engl J Med*. 2020 Dec 24;383(26):2514-2525. doi: 10.1056/NEJMoa2022398.
3. WHO ACTION Trials Collaborators. The World Health Organization ACTION-I (Antenatal Corticosteroids for Improving Outcomes in preterm Newborns) Trial: a multi-country, multi-centre, two-arm, parallel, double-blind, placebo-controlled, individually randomized trial of antenatal corticosteroids for women at risk of imminent birth in the early preterm period in hospitals in low-resource countries. *Trials*. 2019;20(1):507.
4. Althabe F, Belizan JM, McClure EM, Hemingway-Foday J, Berrueta M, Mazzoni A, et al. A population-based, multifaceted strategy to implement antenatal corticosteroid treatment versus standard care for the reduction of neonatal mortality due to preterm birth in low-income and middle-income countries: the ACT cluster-randomised trial. *Lancet*. 2015;385(9968):629-39.
5. Lawn JE, Segre J, Barker P, Smith J, De La Torre I, Stones W. Antenatal corticosteroids to reduce preterm deaths in low-income settings. *Lancet Glob Health*. 2014 Aug;2(8):e446.
6. Bhutta ZA, Das JK, Bahl R, Lawn JE, Salam RA, Paul VK, et al. Lancet Newborn Interventions Review Group; Lancet Every Newborn Study Group. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? *Lancet*. 2014;384(9940):347-70.
7. Vogel JP, Souza JP, Gulmezoglu AM, Mori R, Lumbiganon P, Qureshi Z, et al. Use of antenatal corticosteroids and tocolytic drugs in preterm births in 29 countries: an analysis of the WHO Multicountry Survey on Maternal and Newborn Health. *Lancet*. 2014;384(9957):1869-77.
8. World Health Organization. WHO recommendations on interventions to improve preterm birth outcomes [Internet]. Geneva, Switzerland: World Health Organization; 2015 [cited 2025 May 20]. 98 p. Available from: <https://iris.who.int/handle/10665/183037>
9. World Health Organization. WHO recommendations on interventions to improve preterm birth outcomes [Internet]. Geneva, Switzerland: World Health Organization; 2015 [cited 2025 May 20]. 98 p. Available from: <https://iris.who.int/handle/10665/183037>
10. Hemming K, Taljaard M. Reflection on modern methods: when is a stepped-wedge cluster randomized trial a good study design choice? *Int J Epidemiol*. 2020 Jun 1;49(3):1043-52.
11. Hemming K, Kasza J, Hughes J. The Shiny CRT Calculator: Power and Sample size for Cluster Randomised Trials [Internet]. Available from: <https://clusterrcts.shinyapps.io/rshinyapp/>

