

Expression(s) of Interest

are Invited for Participation in the

PrECISE-Implementation Study

Preterm and LBW Care through Early CPAP, I-KMC/ MNCU, Antenatal Steroids and Early Enteral Feeding (PrECISE): A Multicentric Implementation Research Study

Introduction

The Problem

Preterm birth related morbidity and mortality is a significant global health concern. Approximately 13.4 million babies were born prematurely in 2020, with complications from preterm birth being the leading cause of death among children under five years¹. 81% of the prematurity related neonatal mortality occurs in Asia and Africa². India, which accounts for 22% of global preterm births, faces a substantial burden, with about 3 million preterm births annually¹. Various studies in India show that preterm neonates account for about 20-70% of NICU admissions in the country³. Apart from the heightened risk of dying early, these infants often battle long and short term morbidities like respiratory-distress syndrome and related complications, transient apnoea, hypothermia, hypoglycaemia, patent ductus arteriosus-related heart failure, necrotising enterocolitis, late-onset sepsis, intraventricular haemorrhage, retinopathy of prematurity etc. Those who survive often have a long struggle with bronchopulmonary dysplasia, systemic and pulmonary hypertension, chronic kidney disease, insulin resistance and metabolic syndrome, premature ischaemic heart disease, endocrine dysfunction (e.g., reduced peak bone mass), neurodevelopmental sequelae, permanent visual and auditory impairment and more⁴.

Need for Evidence Based Interventions

The plethora of morbidities, complications and high mortality risk among preterm newborns warrant high quality targeted Evidence-based interventions (EBIs), such as appropriately used antenatal corticosteroids, respiratory support including early CPAP, early enteral feeds, properly delivered Kangaroo Mother Care (KMC) including immediate KMC, Mother Newborn Care Unit (MNCU) for zero separation of the mother and baby. These EBIs have been proven to be individually highly effective in reduction of mortality and improved outcomes among preterm neonates. All of these interventions are recommended as a part of national/ international evidence based guidelines, however it is crucial to assess the impact of these interventions when implemented with high quality and coverage as package of care for small and sick babies.

Evidence-based interventions (EBIs) in newborn care and their present status of implementation

1. **Antenatal Corticosteroids (ACS):** Antenatal corticosteroids when given to pregnant women between 24-34 weeks of gestation with threatened preterm birth are effective in improving neonatal outcomes, and have found to reduce neonatal mortality by 22%⁵. The Ministry of Health and Family Welfare ,GOI has issued Operational Guidelines for the Use of Antenatal Corticosteroids in Preterm Labour, emphasizing their administration under specific conditions⁶. However, both underuse and overuse have been observed in practice which is harmful. Studies identify the need for improved referral services, accurate gestational age assessment, supply chain issues, standardized protocols, and sufficient monitoring mechanisms in improving coverage and quality of ACS. The coverage (of any dose received) ranges from 7-74% across various countries, including Indian tertiary care centres at 69% and secondary care centres at 17%, respectively⁷.
2. **Immediate Kangaroo Mother Care in Mother Newborn Intensive Care Unit (iKMC / M-NICU) and continued Kangaroo Mother Care >8 hours/day (cKMC):** Kangaroo Mother Care (KMC) is a cost-

effective method where preterm or low birth weight (LBW) infants are held in skin-to-skin contact with a caregiver, ensuring exclusive breastfeeding, thermal care, infection prevention and improved growth and development. KMC improves survival of the neonate by 40%, when provided to clinically stable babies⁸. iKMC- which means initiating of KMC soon after birth without initial stabilization, adds a survival advantage of 25% over and above that provided by conventional KMC⁹. ENAP reports suggest that iKMC indicators will be integrated in 32% countries by 2030¹⁰. Encouraged by this new evidence, Government of India has now introduced the concept of MNCUs intended to replace the conventional Special Newborn Care Units (SNCUs) which lead to an unnatural separation of the mother and the baby, paradoxically putting the latter at risk of increased morbidity and mortality. However, the pace of effective implementation of these high quality evidence based interventions is low. Lack of awareness and resistance to change among healthcare providers, cultural barriers, lack of maternal education, have been found as factors hindering their adoption. Some states have initiated in converting the existing SNCUs to MNCU with support from the NHM . Unpublished data from ongoing studies shows a very low coverage of immediate and effective KMC of 8hrs in SNCUs/ NICUs.

3. **Early Enteral Feeding and Rapid Advancement:** Starting enteral feeding early among preterm newborns and advancing it rapidly, improves micronutrient absorption, supports intestinal development and maturation, fosters microbiome growth, minimizes inflammation, and contributes to enhanced neurodevelopment. Strong recommendations exist for starting enteral feeds on the first day of life among preterm (including very preterm, <32 weeks of gestation) and LBW (including very LBW < 1.5 kg) infants. The enteral feeds once initiated should be advanced rapidly, by 30ml/Kg/day or more. It has also been reported that full volume enteral feeds (as per the day's fluid requirement) can be initiated from the first day of life without need for intravenous alimentation or parenteral fluid in stable preterm neonates with gestation age of 28 weeks and more and may be considered¹¹. The daily feed advancements mimic the daily fluid requirement. Conventional practice among health care providers has been to postpone feeding for very preterm babies to after 24h, due to perceived increased risk of Necrotizing Enterocolitis. However, available evidence does not support this. Apart from this, cultural misconceptions about discarding colostrum among mothers and families among the clinicians hinder high coverage of this evidence based practice. The coverage of early enteral feeding within 24 hours in NICU settings is low and ranges from 14-43%^{12,13}.
4. **Early use of Continuous Positive Airway Pressure (CPAP) for Respiratory Distress Syndrome (RDS):** CPAP is a critical intervention for respiratory support in preterm infants. CPAP, in form of bubble CPAP, is recommended in preterm infants with clinical signs of respiratory distress syndrome¹⁴. In some settings, CPAP may be recommended prophylactically for very preterm newborns <32 weeks of gestational age. Despite its proven efficacy in reducing prematurity related mortality and morbidity, its use is limited in resource-constrained settings due to lack of trained personnel, lack of standard operating procedures, associated equipment ,consumables and running costs etc. Facility based newborn care guidelines have introduced recently the use of early CPAP as standard of care at secondary level of care. The availability of continuous positive airway pressure (CPAP) and its use in neonatal units in government hospitals across India revealed that 68.3% of medical college hospitals (MCH) and 36.6% of district hospitals (DH) used CPAP in neonates. The coverage of early use of CPAP is very low¹⁵.

Henceforth, in this document, we will call these 4 interventions the '**PrECISE**' interventions.

Rationale for the choice of Interventions

Health impact of an intervention on the targeted population (preterm newborns) in public health settings is a direct function of- **Proportion of the affected population by a particular cause of death *effectiveness of the EBI * Coverage of the EBI**. Since PrECISE interventions have reasonably proven highest effectiveness, therefore, In a particular context, presence of a large (modifiable) coverage gap makes them a candidate for enhanced implementation utilizing innovative health system interventions (implementation strategies).

Implementation Research (IR) and how it can improve the newborn care

While the importance of efficacy/effectiveness research cannot be overstated, the popular perception that generating knowledge about EBIs will be enough to empower healthcare service providers and would result in a

proportionate improvement in patient outcomes has been proven wrong in the pragmatic world. Implementation Research has played an important role in covering this 'know-do' gap through a variety of implementation strategies. Some examples are, Home Based Newborn Care through community health workers, establishment of Facility Based Newborn Care, Kangaroo Mother Care upscaling, Community Management of Possible Serious Bacterial Infections. By identifying systemic obstacles and tailoring solutions to local contexts, implementation research ensures that life-saving newborn care practices reach those who need them the most.

Research Question

How can 'PrECISE' package of Interventions be effectively implemented to improve survival of LBW (<2500g) and preterm newborns less than 37 weeks of gestational age admitted to NICU/SNCU in various regions of India?

Objectives

1. To develop and optimize multicontext iterative Implementation Models for high quality and coverage of PrECISE interventions for the NICU care of LBW (<2500g) and preterm newborn below 37 weeks of gestational age
2. To study the fidelity, acceptability, adaptability, appropriateness and sustainability of the interventions
3. To study the impact of these strategies on the survival of LBW preterm newborns at discharge from the hospital.
4. To estimate the Incremental Costs of the implementation model.

Study Methodology

Study Setting

Birthing place: Labour room/OT, NICU/SNCU Newborn Care Units and post natal ward

Study population

Study beneficiaries- LBW (<2500g) and preterm newborns <37 weeks of gestation and their mothers/ families
Study Actors/ Implementation Partners- Nurses, doctors, paramedical staff posted at NICU, Labour Room/OT and Post natal Ward, Incharges and administrative heads of these units will lead the implementation of new strategies for EBIs.

Study Teams/ Implementation Research Teams (IR Teams)

The research teams will provide technical inputs to and help in implement the EBIs. The IR team will be composed of three units- 1) Implementation Support Team, 2) Rapid Learning and Feedback Team and 3) Outcome monitoring/ Program evaluation team, all with their distinct roles.

Study Design

Implementation Research Study- With mixed methods (qualitative and quantitative) and quasi-experimental design with an interrupted time series analysis.

Study Phases

The study will span through following phases:- **Formative Phase (3months)** would involve understanding of the implementation status of the EBIs and their determinants, after this a **Co-development phase and initial pilot (6m)** wherein initial implementation strategies will be spelt and implementation will begin. During the **Co - implementation Phase (18m)** the strategies will be further refined based on the iterative Plan Do Study Act cycles. **The Consolidation phase (6m)** will involve continued implementation of the refined model ensuring sustainability. A planned **Exit phase (3m)** will be marked by implementers sustaining the implementation without hand holding by the research team while the evaluation of the EBI implementation continues.

Data collection plan

Pre-Intervention Phase (Baseline):

A continuous baseline phase will precede the intervention across all facilities, during which routine data will be collected for a specified number of time points (e.g., 6-12 months).

Formative research will be undertaken in this phase to understand contextual barriers and co-develop the implementation strategy.

Intervention Phase (Interrupted Point):

The implementation strategy will be introduced at a defined time point, uniformly across all or a subset of sites depending on readiness and feasibility. This marks the interruption in the time series. The timing of the intervention will be clearly documented for each site.

Post-Intervention Phase:

Outcome data will continue to be collected at the same time intervals post-intervention to assess both immediate and gradual trends of the implementation strategy.

Implementation Research Frameworks and models to be used

Consolidated Framework of Implementation Research (CFIR)¹⁶ will be utilized as a determinant framework for understanding and analyzing contextual factors, Implementation Research Logic Model (IRLM)¹⁷ will be used to generate understanding of prospective linkage between determinants of implementation, implementation strategies, the mechanisms of action resulting from the strategies, and the implementation and clinical outcomes affected.

Choice of Implementation Strategies

Though context specific implementation strategies will be co-developed and finalized in consultation with the implementing teams at the sites, a suggestive choice of strategies/ implementation interventions will be listed from Expert Recommendations for Implementing Change (ERIC)¹⁸ list. A CFIR –ERIC matching tool will be used to list most recommended strategies in a specific context.

Study Duration

3.5 years

Outcomes of interest

1. Optimized context specific implementation models which lead to implementation of PrECISE interventions with highest coverage, quality (adoption, adaptation, fidelity) and equity.
2. Inputs, Process Changes (Activities) utilized for development of such a model will be listed and disseminated. The knowledge can be replicated in similar contexts.
3. Outputs in terms of guidelines, policy documents, standard operating procedures, information, education and communication material will be generated, skilled human resources with leadership qualities will be nurtured.
4. Service delivery outcomes-
 - a. % babies born preterm who received antenatal corticosteroids (appropriate use)
 - b. % babies born term who received antenatal corticosteroids (inappropriate use)
 - c. % preterms or LBW infants who received KMC within 1 h of birth
 - d. % preterm or LBW who received KMC >8h/day during entire duration of hospital stay
 - e. % preterms who received enteral feeds within first 24h of birth
 - f. % preterms initiated on full enteral feeds (ETEF -Early total enteral feeding) within 24 hours of birth
 - g. % preterms with respiratory distress who received CPAP within 15 min of onset of distress.
5. Clinical outcomes such as sepsis rates, growth and neurodevelopment, retinopathy of prematurity, long term complications and an overall reduced mortality due to prematurity related complications- the impact outcome. Survival at discharge would be a major outcome indicator along with a choice of other health outcomes which will be finalized.
6. Incremental Costs/ Cost benefit analysis of the model thus developed may be evaluated to inform the policymakers for a more efficient program outlay.

Who can apply:

Permanent faculty in-charge of SNCU/ NICU at Tertiary Care Centres- Medical Colleges/ Post-Graduate Teaching institutes (Public or Private)- will be eligible to apply as Principal Investigators.

The Team should be willing to work towards infrastructure and large equipment purchases (e.g. CPAP machines) for the initiative. ICMR funds will not be applicable for this purpose.

The teams with prior experience in conducting facility (or community) based implementation research studies/ implementation trials especially around maternal and newborn health will receive preference.

The team should have multidisciplinary experts including neonatologists, obstetricians, implementation researchers, methodologists, public health experts, statisticians, data management experts etc.

Application Process

Information to be included in the EOI:

1. Introduction, Rationale and Team Strength (Two Pages)

- A. General Information: Name and Location of the Institution, No. of beds overall, Level of newborn unit, no. of beds in the newborn unit.
- B. Research Team (Principal Investigator, PI along with maximum three co-Investigators)
- C. Rationale of site selection:
 - i. Need for Implementation Research: Baseline values for coverage of process indicators should be enlisted (Data collected for previous three months at least, should be presented, indicating the period of reference)- Please Check the Google Form by clicking on the url below.
 - ii. Readiness for Implementation Research: Availability of space and other resources OR willingness of the PI to work towards identifying space and resources for MNCU in their institution.
- D. Established support from state and district health systems which might be relevant for implementation.

2. Illustrative Budget outline (one page)

Please mention the budget under the following headings: staff, recurring contingency, travel, non-recurring/ equipment, meetings and overhead. (Please refer to ICMR budget guidelines when preparing the budget.)

3. One-page CV of the principal investigator and other investigators (one page CV of upto 3 key investigators)

Please provide a one-page CV of the PI and other key investigators from each identified area. Each CV

should include:

- Academic and professional qualifications
- Current position and affiliation
- Up to five most relevant previous research grants
- Up to five most relevant previous publications
- Experience in undertaking funded projects on neonatal health

4. Application Should be endorsed by Head of Division Pediatrics/ Neonatology as well as Head of the Institution.

Review process:

The EOI documents will be screened for completeness, quality and eligibility by the ICMR. The shortlisted applications will be reviewed by an independent selection committee through predefined selection criteria. The selected teams will then collaborate to develop a detailed proposal, under the guidance of ICMR. The roles and responsibilities of the respective teams will be decided by the project steering committee constituted by ICMR.

How to submit the EOI?

The EOI can be submitted through **ONLINE MODE ONLY** using the Google form through the link given below:

<https://forms.gle/EMPyVB6CPVTyhnES7>

Only the shortlisted applicants will be contacted via e-mail

Important Timelines

Activities	Date
Release of the Call	11.08. 25
Last date for submission of EOI	08. 09.25
Shortlisting of EOIs	25. 09.25
Proposal Development Workshop	13. 10. 25 & 14. 10. 25

For any queries related to the call, please contact the following:

Dr. Amlin Shukla
Scientist E
Implementation Research & Delivery Division
Indian Council of Medical Research
Ansari Nagar,
New Delhi – 110029
Email: amlin.shukla@icmr.gov.in
Phone No.: 8447125128

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