Impact of topical application of cold-pressed sunflower seed oil with improved massage practices on neonatal mortality: a cluster randomized controlled trial in rural North India

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Background & Purpose

Most neonatal deaths are preventable, and occur at home within low resource settings in developing countries, particularly in south Asia and sub-Saharan Africa, against a backdrop of high-risk newborn care practices, sub-optimal care-seeking and weak health systems[1,2]. Emerging evidence suggests that a substantial reduction in neonatal mortality can be achieved with simple, low-cost interventions within family and community settings[3–5]. However, there has been limited success in replicating existing community-based models and thus, impact at scale remains a challenge. In order to accelerate neonatal mortality reduction, there is an urgent need to develop innovative approaches and solutions which are both effective and readily scalable through a combination of public health delivery systems, private enterprise and community demand.

Role of infection prevention in neonatal mortality reduction

The most common causes of neonatal deaths in high-mortality settings are serious infections (29.2%) and prematurity (28.9%), which together account for over 1.6 million deaths annually[6]. Moreover, prematurity predisposes newborns to an increased risk of invasive infections with a case fatality rate greater than 50%. Although little progress has been made in reducing rates of preterm births, interventions targeted at sepsis have proven to be effective in reducing neonatal mortality[7,8]. However, curative approaches towards management of serious neonatal infections have limited feasibility in the context of weak health systems, as they require a high quality trained workforce, measures for skill retention, effective supervision and efficient logistics for drugs and supplies. Moreover, the effectiveness of antibiotic therapy is increasingly threatened due to emergence of antibiotic resistance[9]. Preventive strategies, especially in the context of universally prevalent high-risk practices, are potentially more cost-effective, sustainable, and scalable through existing public health delivery systems[4].

Role of skin in infection prevention

The skin can serve as an important entry point for infections in newborns. Neonatal skin is the largest organ of the neonate's body making up 13% of total body weight, versus 3% in the adult, and provides a large surface area for entry of infectious agents[10]. Augmentation of skin barrier function through topical application of a suitable emollient and reducing exposure to infectious agents through adoption of healthy skin care practices within communities appear to be promising, yet untested strategies for preventing infections and improving neonatal outcomes in developing countries.

Skin barrier function in neonates

Human skin has two distinct but interdependent components: the epidermis (outermost) and the dermis. The barrier function of the skin predominantly resides within the most superficial layer of the epidermis,

the *stratum corneum*, which forms a critical physical barrier, and prevents systemic infection from invading surface micro-organisms and poisoning as a result of absorption of drugs and chemicals; modulates fluid homeostasis and regulates temperature and sensation[10–12]. In utero, the stratum corneum begins to develop around 24 weeks of gestation and is well defined by 35 weeks of gestation. However, development of functional maturity takes a longer time and continues until after birth[10,12]. The developmentally compromised skin in preterm infants, also lacking the naturally protective cutaneous bio-film, the *vernix*, is ineffective as an epidermal barrier and is easily traumatized, providing a portal for invasion by bacteria and fungi[12–14]. Not only premature neonates, but also full-term infants exhibit immature barrier function, manifested as increased rates of trans-epidermal water loss (TEWL), decreased stratum corneum integrity, and an elevated surface pH, which together increase the risk of infection and inflammatory dermatoses[15]. In developing countries, skin barrier function may be further compromised due to intrauterine malnutrition[16], high environmental loads with virulent pathogens and almost universal prevalence of potentially high-risk domiciliary skin-care practices, such as forceful removal of the vernix; continued insult to the skin through regular scrubbing with a coarse paste; vigorous massage, etc. throughout the newborn period; and poor skin hygiene.

Role of emollients in skin barrier enhancement

Topical application of emollient may enhance epidermal barrier function by protecting the stratum corneum, leading to improved skin integrity. Some emollients, such as aquaphor, enhance skin barrier function by forming a protective coating on top of the stratum corneum[17]. Natural oils, such as sunflower seed oil (SSO), have been found to improve the overall condition of the skin and minimize injury, plausibly through metabolism of lipids derived from the fatty acid content of the oil, that are used as nutritional building blocks for the formation of epidermal barrier[9,18].

Current evidence on effects of topical emollients

Studies on mouse models have revealed that oils with a high percentage content of essential fatty acids, particularly linoleic acid, improve skin barrier function. In one study, as compared to controls (no topical application), application of SSO significantly accelerated skin barrier recovery, whereas mustard, olive and soybean oils significantly delayed recovery of barrier function.[19] Mustard oil, a commonly used emollient in large belts of north India, Pakistan and Bangladesh[20], was found to induce an inflammatory response, plausibly due to its allyl isothiocyanate content[21]. Cold-pressed SSO contains about 60% linoleic acid and has been found to be promising as an emollient of choice in hospital settings in Egypt and Bangladesh. When applied to preterm infants (<34 weeks) in Egypt, cold-pressed SSO was associated with a significant improvement in skin condition (skin scoring was based on assessment of skin for dryness, scales or fissures, erythema, crusting or oozing, pustules or vesicles) and 54% reduction in the incidence of nosocomial infections as compared to infants not receiving topical emollient[18].The protective effect of cold-pressed SSO was reconfirmed in another randomized controlled trial in Bangladesh. Cold-pressed SSO when gently massaged on very preterm babies <33 weeks gestational age admitted to the neonatal special care unit led to a 40% reduction in nosocomial infection[9] and 26% reduction in mortality[22] compared to the group that did not receive any oil massage. None of the studies reported any adverse outcomes. However, allyl isothiocyanate, the inflammation-inducing component of mustard oil, has also been reported to have bactericidal and fungicidal properties[23–26]. While studies in animal models point to its adverse effects on skin barrier function, there have been no studies to test the effect of mustard oil on human newborns with respect to infection prevention and mortality reduction. Further, comparative studies of SSO against other oils typically used for infant massage, including mustard, coconut, sesame, oils, etc. have not been conducted on human newborns.

Other reported effects of oil massage

Various studies have shown beneficial effects of oil massage on other developmental parameters as well, including growth, weight gain, neurobehavioral development, thermoregulation and improved sleep, among preterm and low birth weight infants[27,28]. A Cochrane review on effectiveness of massage in infancy concluded that in the absence of any evident harm, the findings from the different studies may be sufficient to support the use of infant massage in the community, particularly where the stimulation of infant is poor[29].

Community perspectives on oil massage

Application of emollients and massage of newborns beginning at birth is traditionally rooted, universally practiced and considered a critical component of newborn care by primary caregivers in South Asia. Oil massage (*abhyanga*) of both the newborn infant and the mother has been given a lot of emphasis in *Ayurveda*, the Indian traditional system of medicine. Mustard oil is used as the most common emollient for newborn massage in large parts of south Asia, including northern India, Pakistan, Nepal and Bangladesh. Mustard oil is readily available, used as a popular cooking oil, grown and processed locally and is the emollient of choice for all age groups. Studies from Shivgarh in Uttar Pradesh have revealed that the perception of benefits of oil massage is deeply rooted. Though specialized caste-based roles (the *domin* and *naun*) for massage exist within the community, newborn massage is commonly given by adult female members of the household. Mustard oil is sometimes pretreated before application by warming and mixing with various condiments. Massage with mustard oil was perceived to be critically important for weight gain and imparting strength to the baby in 83% and 46% of respondents respectively[30]. It is also considered to be beneficial in inducing sleep, strengthening bones and keeping the skin clean. Mustard oil is perceived to have a number of other therapeutic benefits as well e.g., enhancing blood circulation, improving hair growth, protecting the baby against cold, relieving nasal and chest congestion, etc.[31–33]

Evidence gaps

The strong evidence from hospital settings on the effect of SSO on infection prevention and mortality reduction in preterm infants makes a compelling case to test its effect in community settings. However, the hospital studies in Egypt and Bangladesh were conducted on preterm infants, in the absence of high-risk skin care practices, and the impact was compared against a control group of infants who were not at all massaged, in contrast to a community setting, where all newborns are potentially at risk as high-risk skin care practices are universally prevalent, and massage with mustard oil is a common practice. Thus, there are important contextual differences between the emollient therapy provided in the clinical studies as compared to community settings. In order to assess the generalizability of the preventive effects of SSO to community settings, these contextual differences between hospital and community settings need to be recognized, and corresponding evidence gaps need to be addressed in a community trial.

Equipoise

Inferences drawn from existing mechanistic studies are based on skin barrier enhancement as a potential pathway for infection prevention. However, there could be other pathways of infection prevention present in other emollients such as mustard oil, for e.g., constituents with bactericidal and fungicidal properties. Moreover, pretreatment of mustard oil, as practiced in the community, may potentially mitigate the observed ill-effects in the mechanistic studies. Since both these emollients potentially prevent infections through different pathways, it is possible that the impact of massage of newborns using SSO in a community setting with controls using mustard oil may not be comparable to its impact in a hospital setting with controls receiving no emolliation. Therefore, there is equipoise in the two ‘treatments’, thus justifying the need for a community-based efficacy study from an ethical perspective.

Research hypothesis

We hypothesize that all newborns in general and newborns with a developmentally compromised skin barrier in particular, within communities in high neonatal mortality settings will benefit from improved skin care practices and massage using SSO. The primary research hypotheses are:

Promotion of cold-pressed SSO as the emollient of choice coupled with improved newborn massage practices in comparison with standard massage practices in the community will lead to:

- at least 20% reduction in neonatal mortality rate *after 24 hours of birth.* (Based on the current mechanistic understanding of how this intervention works, we do not have reasons to believe that there would be any impact on mortality during the first 24 hours.)

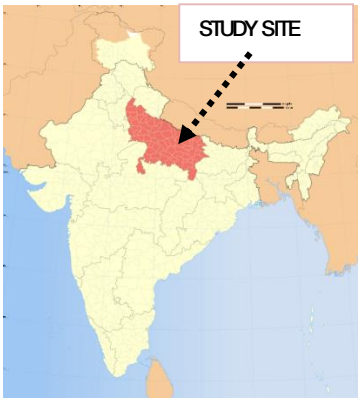
  AND

- at least 15% reduction in neonatal mortality rate. (As we expect the intervention to impact mortality post 24 hours, therefore when we include deaths in the first day, we would expect the overall impact on NMR to be slightly less at 15%.)

Study site characteristics

The study is proposed to be conducted in the Shivgarh region, a contiguous area across 8 administrative blocks spread over 2 districts, Rae Bareli and Amethi, in the state of Uttar Pradesh (UP). The state holds the key to meeting India's millennium development goals and accounts for over 25% of the country's burden of neonatal deaths. The socio-economic and demographic characteristics of UP are similar to larger parts of northern India and greater part of south Asia e.g. Pakistan, Nepal and Bangladesh. This region is characterized by weak health systems, poor care-seeking for newborn illnesses and predominantly community-based traditional form of newborn care. This region is also characterized by very high rates of neonatal mortality, mostly within the home due to preventable causes and associated potentially high-risk domiciliary newborn care practices. Newborn skin care practices including near-universal use of mustard oil for infant massage are similar across UP and the entire region. Thus, research findings in UP can be generalized to other high-mortality states in India and neighboring countries.

Several newborn health studies have been conducted in Shivgarh including a randomized controlled trial evaluating the impact of behavior change interventions on neonatal mortality reduction. The findings of the studies have been rapidly integrated into the National Rural Health Mission in UP and continue to provide evidence to the government, informing its programs. The proposed trial will however, exclude areas that have been part of previous trials. Community partnership, relationships with government officials, and research infrastructure at Shivgarh will be leveraged for this trial. The proposed trial will cover a population of about 800,000 spread over 276 Gram Sabhas (village administrative units) in 8 administrative blocks.



Study Area	
Population	840,000
Scheduled Caste (%)/ Below Poverty Line (%)	35.3 / 43
Crude Birth Rate/Annual Birth Cohort	27 / 22,572
Institutional Delivery (%)	84
Massage during early neonatal period (%)	97
Use of mustard Oil as an emollient of choice (%)	98
Neonatal Mortality Rate (per 1000 live births)	45

Table 1

Community Health Intelligence Platform (CHIP)

The trial will be conducted in an area where an epidemiological observational study, Alliance for Maternal and Newborn Health Improvement (AMANHI) to measure burden and risk factors for maternal and neonatal mortality and morbidity, is in progress. The Community Health Intelligence Platform (CHIP) developed as part of AMANHI, involves early identification of pregnant women through a 2-monthly prospective pregnancy surveillance of all women in the reproductive age group and notification of deliveries within one week of birth. Based on surveillance and notification, three antenatal visits (24-28 weeks, 32-36 weeks and 38-40 weeks of gestation) and two postnatal visits (1-6 days and 42-60 days after birth) are being conducted. Deaths among all women in the reproductive age group and among newborns are being recorded. Verbal autopsy interviews are being conducted to determine the timing and causes of all deaths of women during pregnancy, childbirth and postpartum period; and also for stillbirths and neonatal deaths. Due to common study area for AMANHI and the trial and synergies in evaluation process, the existing platform of CHIP will be leveraged towards the evaluation of the trial. This would also minimize information bias, as data is already being collected in a uniform and standardized manner across the study area. Additionally, enhancements in the existing platform would be made to meet the trial specific requirements.

Design of the intervention

The proposed community-based intervention consists of the following aspects:

a. The technical intervention package, which is the final intervention that must be provided to newborns in the intervention clusters, and is hypothesized to lead to an improvement in newborn survival

b. The intervention delivery strategy, which is the entire process through which the technical intervention package will be introduced into the community and to families, and maintained in order to ensure that it is received by newborns in the intervention clusters

c. All measures to ensure intervention monitoring and compliance, that are specific to the intervention clusters, and are meant to increase coverage and uptake of the intervention as per the recommended protocol

Technical Intervention Package

The technical intervention essentially consists of:

(a) the product, i.e. cold-pressed sunflower seed oil, and

(b) accompanying directions for newborn massage. The “directions for newborn massage” further consist of the following aspects:

i. Dosage of SSO, comprising of frequency of use, quantity per use, and duration of use.

ii. Improvements in overall massage practice, such as hand-washing prior to massage and ensuring hygiene during massage, delaying the use of mustard oil and scrubbing substances past the newborn period, etc.

The first aspect has been derived from massage protocols that were followed in the hospital-based studies in Bangladesh and Egypt [9,18,22]. The second aspect has been derived from an understanding of existing massage practices from the perspective of the above-mentioned risks, based on formative research in the community.

Intervention	Description
Application of SSO	Emollient Product: cold pressed SSO Dose: 10g per application, applied 3x daily Duration: 0-27 days of life
Improved massage practice	- Encourage hand washing prior to massage - Encourage gently massaging the vernix into the newborn skin, rather than forcefully removing it - Promote gentle massage of newborns - Delay use of mustard oil and skin-scrubbing substances such as *bukwa* (coarse-grained paste made of mustard/wheat seeds along with additives) past the newborn period - Ensure that the newborn is kept warm during and after massage

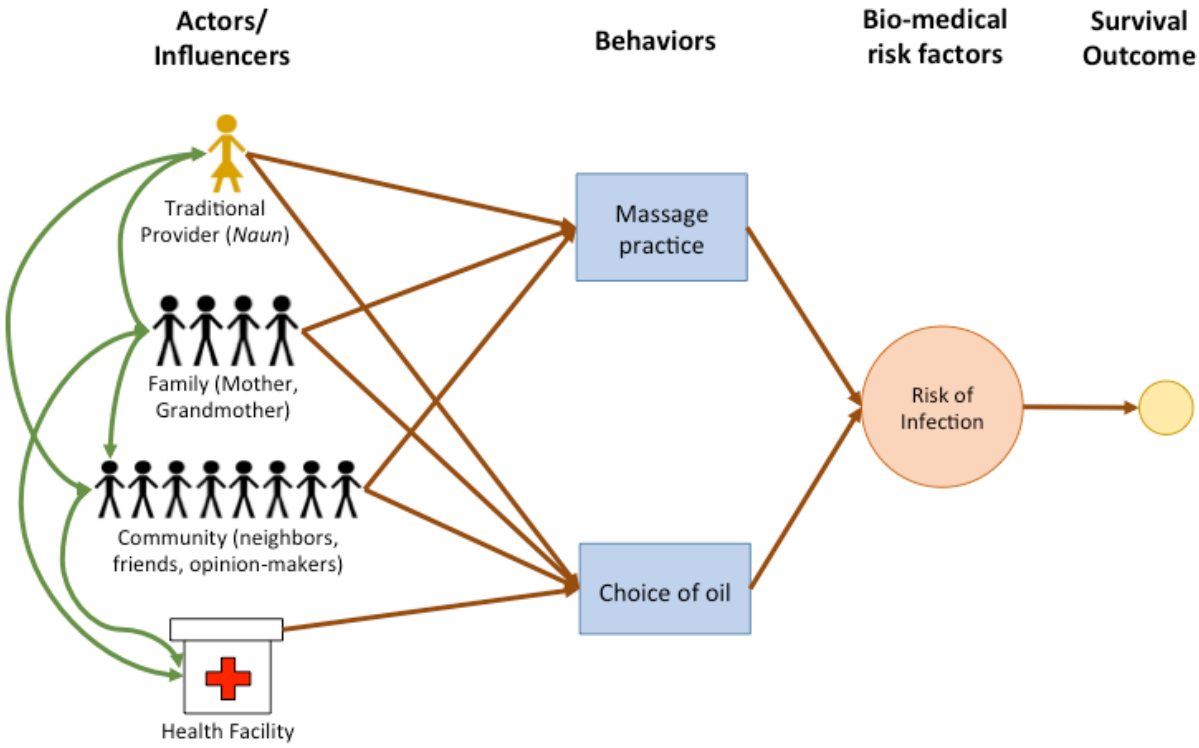
Table 2

Intervention delivery strategy

The following principles guided the development of the intervention delivery strategy:

- As this is an efficacy trial, every plausible effort must be made to maximize the uptake in the intervention clusters. Therefore early intervention, high coverage, equity and quality of behavior change interactions/ massage training must be ensured.
- Contamination to control clusters must be prevented and minimized to the extent possible.
- The delivery strategy should ensure that the intervention received by newborns in the intervention clusters should ONLY consist of the proposed technical intervention delivered in a standardized manner, ensuring that no other interventions with potential effect on newborn survival are selectively introduced only into the intervention clusters in order to ensure integrity of trial design.
- Infant massage is a deeply entrenched traditional practice with *nauns* as its flagbearers. Given that the outcome of the trial is not known *a priori*, ethical and responsible engagement and dissemination of information to nauns and families is important.

We adopted the Behavior Change Management approach[34] in order to develop the intervention delivery strategy. We identified all 'actors' who perform or influence the practice of massage and choice of oil in the community. The primary practitioners of newborn massage in the family are the mother and grandmother. However, the practice of newborn massage is a deeply institutionalized practice in the community, with special caste-based traditional cultural roles for providing massage to the mother and newborn during the first few days after delivery. These are the *nauns* and *domins*, who collectively, have near universal coverage in the community for providing postnatal massage services. Due to the increase in institutional deliveries (~84% in this community) as a result of the introduction of the Janani Suraksha Yojana program by the government over the last few years, government health facilities are also a potential influencer. In facility births, the first oil application on the newborn is for the purpose of vernix removal (in response to community demands), and is done with the mustard oil provided to the nurse by the family.



Schemata showing the "Causation Pathway"[x] for massage-related behaviors

Amongst these, the *nauns* (or similarly preferred traditional masseuses) emerge as the agents of choice to intervene at the family level for the following reasons:

- They are considered as experts in traditional postnatal massage in the community, and therefore in a position of authority to affect behavior change
- They are called upon by the family soon after delivery for initiating maternal and newborn massage and continue to provide massage for the first 9-15 days. They therefore have the opportunity to negotiate behavior change at the very inception, and train mothers and grandmothers in the massage practice during this period
- They would be common across intervention and control clusters with similar visitations, etc., and therefore this choice would minimize bias due to Hawthorne effect
- As they are not "health workers" in a medical sense, any advice or intervention on newborn health aspects other than massage that they may provide, would be similar in both intervention and control clusters

At the same time, in order to support the *nauns* in promoting the new practices, an enabling community environment, and endorsement and support from opinion-makers would be critical. Moreover, endorsement from health facilities in the use of the new oil would be an important factor in influencing the adoption of the given oil by families. As health facilities are common to intervention and control clusters, this would need to be carefully calibrated to ensure that they accept the oil provided by the families (which would be SSO and mustard oil respectively in the intervention and control clusters) for application on the newborn, instead of enforcing their choice on the family.

Therefore, at the community level, a "*naun* coordinator" would be needed in the intervention clusters to accomplish the following:

i. Interface with *nauns*:

   a. Coordinate training and standardization of *nauns* in the new massage practice and behavior change management skills

   b. Provide ongoing support and necessary supervision to *nauns* to facilitate adoption of new oil and new massage practice

   c. Provide emergency oil supplies to *nauns* on a regular basis

ii. Interface with families:

   a. Administer consent and provide initial supply of oil to pregnant women in their 24th to 27th week of gestation, and intending to reside in the intervention clusters during the newborn period. This is to ensure that families have an initial supply of oil that can be used soon after birth. This is also a suitable opportunity for promotion of exclusive uptake during the newborn period and early negotiation of barriers to change.

   b. Coordinate timely provision of oil supplies to families

iii. Interface with the community:

   a. Conduct regular community meetings (frequency to be finalized as part of TIPS) with key stakeholders to address queries, clarify doubts, share experiences and ensure their support in promoting the new oil and new massage practice

iv. Interface with health facilities:

   a. Ensure that care providers in health facilities do not enforce their choice of oil on families

Engagement with nauns:

Nauns are a caste-based role as flag-bearers of the age-old tradition of massage, with the transmission of knowledge and skills related to massage being passed from generation to generation. They are important community-based stakeholders and influencers for newborn care practices and behavioral change, yet they have been relatively untouched and disengaged with the formal public health delivery system, and therefore their practices have remained largely unchanged. However, with market forces at play and availability of different oils for infant massage in the market, such as Johnson's Baby Oil, Dabur Lal Tel, Olive oil brands, etc., sometimes reinforced by local health service providers, coupled with growing community aspirations, acceptability of new oils has been increasing. However, mustard oil continues to remain the predominant oil in the first half of the neonatal period (0-12 days), with other oils, if any, gradually introduced in the next half. Our aim, in this trial, is to use a proven oil to also influence and improve the massage practice, through the paradigm "newborn, new oil, new practice".

The key things that need to be explored for ensuring participation and ownership of the intervention and behavior change at the family level by nauns are: (1) their openness to the new oil and massage practice, (2) their ability to retain knowledge and skills passed on to them through the training, and (3) their ability to influence families and train mothers and grandmothers in the improved massage practice.

Based on formative assessments, we have found that nauns are more open to adopting a new oil than changing existing practices. Therefore, for greater acceptability, the recommended practice should focus on improving (such as ensuring hygiene), rather than radically changing the practice. Further, to enhance their ability to retain the new knowledge and skills, an extremely simple participatory curriculum will be designed. The intervention strategy and training content will be co-developed and finalized with a representative group of nauns. As experienced in previous behavior change studies, songs are a potent means of retaining and transmitting knowledge, and we will use songs in this study as well. Training

curriculum of nauns will also include a component on behavior change negotiation with families. The entire training package will be finalized after TIPs.

Information provided to nauns:

Nauns will be made to understand that the intervention aims to build on their strengths to improve their practices, and not to replace them. The information provided to nauns would be tailored based on the socio-cultural context. For example, nauns could be oriented to the trial by mentioning 'Just like oil can enter the body through the skin and orifices (as per their belief system), similarly, so can illness. Our aim is to collectively understand and improve our massage practice, so that only oil enters the body, but illness does not.' Regarding the oil, nauns will be made to understand that the given oil (i.e. cold-pressed sunflower seed oil) is completely natural and pure, safe to use and very good for the newborn skin, easily absorbed by the body, and has been found to be effective in preventing infection in hospitals. We aim to test if the benefits of this oil can be replicated in community settings. In order to avoid contamination with commercially available sunflower oil, we do not aim to disclose the name of the oil (i.e. sunflower oil). We will further emphasize to families that the oil has been specially developed for use on newborn skin and should not be used for other purposes such as cooking. The final version of the culturally contextualized communication will be designed with inputs from nauns during trials of improved practices (TIPs).

Prior to initiation of the trial, all nauns in intervention area will be identified and mapped. Orientation meetings will be held with groups of nauns to ensure their ownership and participation. Subsequently, nauns will be trained in batches on the intervention as well as behavior change negotiation and transfer of skills to families.

Nauns will be mentored and monitored by the naun coordinator, who will be employed by the study. Typically, each family already has a long-standing relationship with a naun. The naun coordinator will ensure that each family has been linked up with a naun in the service area. The naun coordinator will conduct direct observation of massage sessions in 5% of each naun's visitations for the first 3 months (during intervention phase-in), until they are standardized. Thereafter, we will conduct independent quality monitoring regarding massage practices and transfer of skills by nauns, from 5% households at random to check for compliance. We have budgeted for a nominal incentive of Rs.150 per baby for nauns. The modalities for payment of incentives will be finalized based on inputs from TIPs.

Oil Supply Logistics:

Mothers will be provided the first supply of oil in the 24th – 27th week of gestation based on their intent to deliver in the intervention area. This is to ensure that intervention begins as early as possible for preterm babies. Prior to delivery, unused oil will be replaced every 3-4 weeks to ensure that the oil does not get stale. Post-delivery, oil supplies will be replenished on a weekly basis. A special logistics team would be set up to ensure timely delivery of oil supplies.

TIPs will be conducted before intervention phase-in in order to review and fine-tune the intervention delivery strategy, procedures for monitoring and compliance, oil supply logistics, etc., to ensure alignment with the guiding principles for intervention design mentioned earlier. TIPs will validate the robustness of the development process and its underlying assumptions, and will be conducted in select villages not included in the proposed study.

Quality control, monitoring and compliance for SSO use

Cold-pressed sunflower oil will be sourced from local manufacturers in India, who will be selected based on lab-based analyses on the lipid composition of the oil (linoleic acid content above 60%), absence of impurities, etc. The oil will be packaged in 10ml barcoded single-application sachets and stored at 4°C to prevent degradation. Random samples of oil from each batch of supply from the manufacturer(s) will

be analyzed in a QA laboratory for its physical and biochemical properties to ensure compliance with quality parameters.

A special logistics team will be set up for coordinating the supply chain of cold-pressed SSO and monitoring its use by families. Used oil sachets along with a brief questionnaire regarding oil use will be collected from families, and fresh supplies provided free-of-cost on a regular basis by the oil supply logistics team. The feedback on oil use will be reviewed by the intervention delivery team to improve efforts for increased uptake.

Trial design

The trial is designed as a public health efficacy trial. The intervention will be evaluated using a 2-arm cluster randomized controlled trial design. A cluster design has been chosen, as the intervention will be delivered through multi-level engagement with families and community stakeholders within intervention clusters, and therefore individual randomization is not possible. The cluster unit chosen for the study is the gram sabha, which consists of a cluster of hamlets and is the smallest self-contained unit of village administration, with an average population of 3,000. Its size is optimal from the perspective of maximizing power and minimizing contamination. During the process of randomization (described later), the entire study area will be randomly divided into 2 equal groups: intervention and control. The intervention to be provided in the intervention arms has been described in detail in the previous section.

The control group will maintain the status quo and receive standard massage practices including oil. These are described here. While mustard oil is the emollient of choice, other commercially available oils such as Dabur Lal Tel and Johnson's baby oil are also used to a lesser extent in the second half of the newborn period. Forceful removal of vernix is a universal practice, using mustard oil in health facilities, and various potentially damaging substances including detergents in the case of home births. Vigorous massage with mustard oil, that is typically heated with condiments such as garlic, fenugreek and asafetida is a universal practice. Babies are typically massaged at least 3 times. The first massage of the day, provided by nauns during the first 9-12 days after delivery, consists of *bukwa* paste (made of wheat flour in summer and ground mustard seeds in winter) application and rubbing to cleanse the baby, followed by vigorous massage, irrigation of body orifices with oil, and 'exercises' for the baby. Subsequent massages during the day are provided by family members including the mother and grandmother of the baby, and typically exclude *bukwa* application. The practice is continued by the family for at least a year, although the frequency of massage may decrease over time. There is a natural variation in practices across nauns and families.

Access to health facilities will be similar in the 2 groups. Care would be taken to ensure that we restrict the difference between the 2 groups to only the intervention (i.e. oil and massage practice), with all other factors including engagement with frontline health workers, etc. remaining the same across groups.

Trial endpoints

Primary outcomes

A) NMR post-24 hours of birth or the number of neonatal deaths that occur after 24 hours of birth, per 1000 live births.

B) Neonatal mortality rate (NMR) or the number of neonatal deaths per 1000 live births.

Secondary outcomes

A) Infections and hospitalization:

Signs and symptoms of infection during the newborn period, alongwith episodes of hospitalization would be recorded through parent recall. These will include local infections such as pyoderma and umbilical cord infection..

B) Growth:
Weight of the baby as close as possible to birth (Day 0) and on Day 28, would be measured through standardized infant weighing scales and procedures.

C) Mechanisms:
Mechanistic studies will be conducted on a random sub-sample (5%) of babies from both arms on days 1, 3 and 7. These include studies to understand the biological effects of the intervention on newborn skin. The aim of studying mechanisms is also to attempt to find potential markers that may be used to test the protective effect of oils alone. The parameters that would be included are:

- Videography of massage to document variations in practice
- Skin barrier function: Barrier property of Stratum Corneum (assessed as trans-epidermal water loss or TEWL)
- Neonatal skin scoring using an appropriate scale (for example, the scale used by Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN), or the Neonatal Skin Risk Assessment Scale for predicting skin breakdown in newborns).
- We will also explore the use of high resolution imaging techniques to assess skin condition.

D) Dose – response:
Any relationship between the exclusive application of provided oil, and the duration and frequency of massage practiced by the family, and the morbidity and mortality outcomes will be assessed.

E) Intervention coverage:
We will measure the percentage of mothers/ families that were reached through the intervention delivery strategy, received the intervention through an accredited *Naun* and received sufficient oil supplies.

F) Changes in practices:
We expect the neonatal mortality in the intervention arm to be reduced through changes in practices related to newborn skin care, massage and oil use. Therefore changes in these practices is an important process outcome of the study. We will also measure other key newborn care practices including care-seeking, which are not hypothesized to be different between the intervention and control arms.

G) Adherence to Intervention:
Information on continued oil use and adherence to massage technique would be obtained from families (mothers). This would also be applicable to a sub-sample (5%) of the population.

Sample size

In order to minimize potential contamination and align with existing geo-political-administrative structures of governance, the *Gram Sabha* (a cluster of villages with ~ 3000 population) is proposed to be the unit of randomization/cluster. A *gram sabha* is the basic geo-political and administrative unit for village-level health planning and implementation.
The sample size formula used is (Hayes & Bennett) for unmatched randomized controlled trials[35] :

$$c = 1 + \left(z_{\alpha/2} + z_{\beta}\right)^2 [(\lambda_0 + \lambda_1)/y + k^2(\lambda_0^2 + \lambda_1^2)]/(\lambda_0 - \lambda_1)^2$$

Where c is the number of clusters in each arm, k is the coefficient of variation (SD/mean) of the true rates between clusters within each group, z_α and z_β are standard normal distribution values corresponding to upper tail probabilities of $\alpha/2$ and β respectively, λ_1 and λ_0 are the true NMR rates in the presence and absence of the intervention, y is the number of person-years of follow up in each cluster.
Sample size calculations to test the hypothesis are done for the two primary outcomes as follows:
Primary outcomes:

1. Neonatal mortality rate (NMR) – To detect at least 15% reduction in intervention compared to control arm
2. NMR post-24 hours after birth – To detect at least 20% reduction in intervention compared to control arm

Assumptions	Primary Outcome	
	Neonatal Mortality Rate	Neonatal Mortality Rate post-24 hours after birth
Avg. NMR (conservative estimate)	45 per 1000 live births	25 per 1000 live births
Range of NMR (w/o intervention)	36 to 54 (±15%)	20 to 30 (±20%)
Expected NMR (with intervention)	38 per 1000 live births (Intervention arm)	20 per 1000 live births (Intervention arm)
Avg. population per cluster	3000	3000
Enrolment & Intervention period	2 years (24 months)	2 years (24 months)
Loss to follow-up	8%	8%
Desired power	90%	90%
Desired significance level	5%	5%
Inter-cluster coefficient of variation (k)	0.10	0.10
Expected number of neonates(per cluster during the intervention period)	162	162
Expected no. of neonates recruited per cluster(accounting for loss to follow up)	149	149
Number of clusters required per arm	138 clusters (~20,536 newborns)	132 clusters (~19,686 newborns)

Table 3: Sample size calculations

(k has been estimated using the methods described in literature[36]. It is relatively small, as all clusters will be rural villages located in the same region, and therefore expected to be similar. Moreover, restricted randomization will contribute to a lower value of k.)

Therefore, 138 clusters per study arm will satisfy the sample size requirement for both the primary outcomes, and hence is the sample size of choice for the trial.

Accordingly, the design effect DEFF may be calculated as:

$$\text{DEFF} = \frac{\text{Cluster}_n}{\text{Individual}_n}$$

where $\text{Cluster}_n = c \times n$, and $\text{Individual}_n = \left(z_{\alpha/2} + z_{\beta}\right)^2 (\lambda_0 + \lambda_1)/(\lambda_0 - \lambda_1)^2$ (as defined [35])
With the estimated value of k = 0.1, DEFF= 1.07

Target group and Eligibility criteria

Clusters

All clusters that are randomized and allocated to any of the study arms will be included for analysis.

Individuals

Inclusion criteria: All newborns (or neonatal deaths) identified in the study area till 7 days of delivery irrespective of place of delivery will be considered as eligible for analysis of trial outcomes. The inclusion criteria would be met in the community, in the following conditions:

1) mother stays through the antenatal period and delivers in the study village;
2) mother delivers outside the study village (e.g., maternal home or health facility) but returns to the study village within the first 7 days of delivery.
3) In case of maternal deaths, newborns identified in the study villages within 7 days of delivery.

Thus, all women/babies who are found to be residing in a particular cluster at the time of first identification during the first 7 days of delivery will be analyzed as part of the same cluster, irrespective of migration or place of delivery, as per principles of intention to treat.

Exclusion criteria: None. All babies fulfilling the inclusion criteria will be included in the study.

Enrolment & allocation

The enrolment strategy is aimed at enabling maximum number of eligible women to participate in the study.

<u>Enrolment and consent for data collection (uniform for both study arms):</u>

The process of enrolment for data collection will be the same in both study arms and follow the scheme of the AMANHI-CHIP platform. The AMANHI-CHIP platform includes a 2-monthly cyclical surveillance system for identification of pregnant women, system of informed consents and follow-up of pregnant women for delivery outcomes. In AMANHI, all efforts are made to enroll women as early as possible during their pregnancy and the same strategy will be followed for the proposed trial. Early identification would ensure that pregnant women are followed up for delivery outcomes (e.g. premature deliveries or abortions) and errors in self-reported LMPs (which are not clinically confirmed in community settings) do not lead to missed outcomes.
In addition, women who are not identified through the Pregnancy Surveillance System (PSS) but are identified after birth to be residing in a study cluster within the first 7 days of delivery, will be consented and enrolled at the time of identification. Operational details regarding pregnancy identification and delivery notification and other aspects of data collection are detailed subsequently.

Allocation to study clusters: All enrolled women will be allocated to the study cluster where they are found to be residing at the time of postnatal identification during the first 7 days of delivery.

Enrolment and consent for intervention (in the intervention arm):

The *naun* coordinators would visit pregnant women in intervention clusters between the 24th and 27th week of pregnancy. Informed consents from only those women with an intention to stay in the intervention clusters during the newborn period (first month after birth) would be taken. An initial supply of SSO will be provided to these women to ensure that they have adequate supply of oil to be used during the early hours of birth, possibly before their delivery has been tracked/notified. This strategy is especially relevant for preterm births given that current evidence through hospital-based studies has shown that the effect of SSO on mortality reduction has been observed in this sub-population of newborns.
All mothers/newborns that have been identified to be residing in the intervention clusters after birth in addition to the above, will be administered consent for use of SSO, and provided the SSO supplies that will be replenished at regular intervals during the newborn period.

Randomization, allocation and masking

An appropriate randomization scheme must be chosen in order to avoid any baseline imbalances between groups. In this study, restricted randomization approach will be adopted to ensure balanced allocation.
The following cluster-level factors are expected to be important correlates of the primary outcomes on which we intend to achieve balance between the study arms. Data for this purpose will be sourced from the existing health intelligence purpose under AMANHI.

- Number of Households in each cluster: This needs to be balanced in order to achieve similar number of participants for each arm.
- Religion (Muslim Population): Muslim population forms a small percentage of the population distribution (11.1%) and hence randomization will be restricted to balance it across the study arms.
- Caste (Schedule Caste population): The population belonging to the scheduled castes (35.3%) is the considered to be the highest-risk because of poor socio-economic status and access barriers. Restricted randomization will balance the total SC population composition in the intervention and control arms.
- Baseline NMR: Baseline estimates of NMR from the AMANHI study will be calculated for each cluster. Baseline NMR is expected to provide a summary measure of all possible pre-intervention factors that could contribute to the primary outcome.

Restricted randomization will be done as follows. A series of random pairs of sequences will be generated, and only the sequence-pairs satisfying the set of restriction criteria will be considered for the allocation process. Restriction will ensure that the distribution based on cluster population, religion, caste and NMR across the two study arms is similar (similar mean as well as standard deviation across study arms), and the clusters are evenly distributed in the geographical area. This method is aimed at reduction of between-cluster variation and will therefore increase the power of the trial.

The first step in the allocation process would be to randomly choose one sequence-pair from the selected sequence-pairs generated through the restricted randomization simulations. In a second step, the two groups will be allocated to “intervention” and “control” arms. The entire process of restricted randomization and allocation to intervention and control clusters would be done independently at WHO, Geneva.

Masking and measures to reduce bias

Since this is a community-based trial, true masking is not possible. However, in order to minimize bias, the following measures would be taken:

1) Randomization (as previously discussed)

2) Using existing community based massage agents, and not community health workers:

   The intervention design uses existing traditional massage providers and not CHWs. Hence, the intervention is layered on existing cultural practices. This would ensure that the only difference between the two study arms is the intervention itself, and no other peripheral interventions affect the outcomes. This will also neutralize Hawthorne effect.

3) An independent evaluation system which is uniform across the study arms:

   Intervention delivery and evaluation would be conducted by two separate and independent teams. Care would be taken to ensure that the evaluation process (including surveillance, follow-up for outcomes, field instruments, data collection visits and quality assurance mechanisms) is uniform in both study arms. Independent evaluation will operate through the following steps:

   - The principal investigating team would be split into two sub-teams, where one team would only be responsible for intervention design and implementation, and the other team would be responsible for outcome evaluation and data management.
   - The quality assurance teams for intervention and evaluation components will be separate.
   - The members of each sub-team would follow its respective reporting hierarchy.
   - Measures to ensure physical separation between the two sub-teams would be taken, both in the field setting and at the central research office in Lucknow.
   - Pregnancy identification and delivery notification from both intervention and control clusters, would be facilitated through a common, independent "call centre" (discussed further) to maintain equal flow of information from both study arms.

4) Masked analysis: The team analyzing the data will be blinded to allocation of the two study arms.

Data collection

Baseline Data:

Baseline data will be sourced from AMANHI-CHIP platform, especially data that will be used for the randomization process.

Concurrent Data Collection:

Underreporting of neonatal deaths is a well-documented problem with retrospective methods of data collection. Therefore, in order to establish accurate measures of neonatal mortality rate, we will be prospectively following up the study population. This is in continuation with the established Pregnancy Surveillance System at CHIP. This has been elaborated later in this section.
Concurrent data collection will involve follow-up of all enrolled women for pregnancy and delivery outcomes as per planned schedule (discussed in the table below).

Data collection timeline	Description of data collected

Baseline and enrollment form [24-25th week of pregnancy]	- Attitudes and intent regarding newborn skin care practices, along with pregnancy history, socio-economic status etc.
Baseline form of the baby [Neonatal visit on Day 0/1]	- Vital status of the baby - Initial newborn skin care practices (incl. vernix removal and massage technique) - Emollient use - Baseline baby weight and gestational age - - Antenatal care practices
Neonatal visit on Day 7	- Vital status of the baby - Newborn care practices (e.g. bathing, feeding) - Emollient use - Baby's health (including hospitalization, skin infections, respiratory problems) - Hygiene (handwashing practices) - Baby weight - Antenatal care practices

Neonatal visit on day 28	- Vital status of the baby
	- Serious adverse events
	- Infant weight
	- Delivery and postnatal care
	- Newborn care practices
	- Skin care practices
	- Emolliation and emollients
	  - Observational data (where possible)
	  - Nature of oil, source of procurement
	  - Source of procurement, processing, pre-application processing
	  - Frequency, duration, community massage providers
	  - Reported benefits or harms
	- Care-seeking
	- Signs and Symptoms of infection (reported by parents)
	-

In case of stillbirth/ neonatal death	- Neonatal verbal and social autopsy

Table 4: Visitation schedule for concurrent data collection

Data collection timeline	Description of data collected
Neonatal visit on Day 0/1	- Skin barrier function: trans-epidermal water loss or TEWL - Neonatal skin score - Videography
Neonatal visit on Day 3	
Neonatal visit on Day 7	

Table 5: Visitation schedule for mechanistic studies for random sub-sample (5%) of the population

Such an intensive data collection system involves setting up the study site, establishing systems for pregnancy surveillance, delivery notification, planned visitations, notification of adverse pregnancy outcomes and maternal and newborn deaths. This is described in detail in this section.

A) <u>Study site:</u>

The study site has already been setup as part of the AMANHI study. This includes:
- Identification of all the gram sabhas and hamlets (human settlements) in the study site
- Physical mapping of all hamlets to ensure that no household is left out and to enable assigning "addresses" to structures for facilitating follow-up
- Listing of all structures and households in each hamlet
- Enumeration of all women in the reproductive age group for prospective follow-up

In addition to the AMANHI setup, mapping and listing of *Naun*s in the entire study area, and their respective catchment areas will be done.

B) Pregnancy identification and delivery notification system:

a) Pregnancy surveillance and tracking (existing through CHIP):

A system of surveillance has been setup, where every household would be visited in a cyclical manner, once every 2 months, for identification of pregnancies, their enrolment and follow-up, and notification of deliveries and their outcomes.

b) System of key informants for delivery notification (existing through CHIP):

A network of key informants such as ASHAs, local birth attendants, elderly women, health facilities and families of pregnant women etc. has been setup for early notification of deliveries.

c) Call-center:

There will be a common call-center for pregnancy identification and delivery surveillance for the entire study area, irrespective of intervention or control. The call center will interface directly with the data management center. The incoming information to the call center will include detected pregnancies and pregnancy outcomes, delivery outcomes and mortality data from different sources (communities, facility staff, study workers (other than pregnancy surveillance workers) and key informants). In addition, the call centre will also play the role of following up pregnant women to track deliveries, monitor visitations by evaluation workers, and enable notification of adverse pregnant outcomes.

All the information (from pregnancy surveillance staff, delivery notification systems, key informants and call centre) will be channelized and consolidated at the Data Management Centre. This information will be fed directly from the data management center to the evaluation team for enrolment and scheduling data collection visitations, and to the intervention team for coordinating intervention delivery. This uniform system of information transfer will minimize reporting bias from the study clusters.

C) Scheduling visitations to follow-up study participants:

The Data Management System will auto-schedule postnatal follow-up visitations based on information obtained on delivery date.
There would be some cases where pregnancies would be identified but there after the women may not be traceable, and their pregnancy outcomes would not be established. These cases would be treated as “loss to follow-up”. However, uniform data collection processes would enable equal monitoring and follow-up of all women, in both study arms.

D) Notification of adverse pregnancy outcomes:

During each of the follow-up visits, adverse pregnancy outcomes (abortion, stillbirth, neonatal death, maternal death) will be recorded. In addition, adverse pregnancy outcomes may also be notified through the call-center.

Data collection and data management process

Data will be collected on Android-based tablet devices, with inbuilt checks of missing values, range inconsistencies, skip patterns, etc., as well as capturing GPS locations at the point of interview. The data will be checked at an aggregate level for heaping, interviewer-specific patterns, etc. Forms

identified with errors will be sent back for verification and re-entry, but audit-trail will be captured to ensure that the full trail from original data and changes there from, is maintained with timestamp, GPS and user information.

Tracking and following-up a large birth cohort of ~40,000 babies in a population of ~800k would involve a huge dataset, and require a robust data management system that ensures data quality, security, timeliness, availability and ease of reporting and analysis. A web-based data management system with end-to-end electronic data flow from data collection to analysis has several advantages over traditional paper-based data collection: it ensures all the above features, including stringent data quality measures and real-time data availability, and at the same time, is more cost-effective than large-scale paper-based data collection as it reduces errors and eliminates costs incurred in printing, transportation, data entry, re-entry/error rectification, and transport and storage of forms.

Data will be stored in a MySQL enterprise relational database management system, tagged with geo-spatial and temporal attributes which will be maintained real-time on the database server and made available through a secure internet website. All data collection instruments used by the evaluation team will be programmed as app-based forms with built-in quality checks. On-site quality assurance would involve both real-time data checks as well as GPS verification of the location of data collection. Data access will be restricted by users, with different privileges for data collectors, supervisors, program team and study investigators. Only selected monitoring data, for e.g., pregnancy and delivery notifications, intervention coverage and uptake will be made available to the program team supervisors for monitoring, reconciliation, quality assurance and feedback to improve intervention delivery and compliance. All personal identification information including names, etc. will be encrypted, and only a unique identification number to identify individuals will be made available for analysis.

Data quality assurance

Data quality assurance holds supreme importance in a randomized controlled trial, and strict measures will be enforced to ensure rigorous standards of data quality, including:

- Training, standardization and close monitoring of data collectors for compliance to performance and quality benchmarks.
- Real-time GPS tracking of point of data collection
- Online real-time checks for missing values, inconsistencies, skip patterns, etc. built-in to the software
- Random spot checks: Supervisors will make random visits in 5% of households covered by each data collector to observe the process of data collection
- Back checks: Supervisors will validate the data collected with 10% households per data collector (Discrepancies will be resolved through re-visitation and re-administration of entire questionnaire by supervisor.)
- Re-interviews: Supervisors will re-administer the data collection instrument randomly to 5% of households covered by each data collector. (In case of discrepancies, data collected by supervisor will be used.)
- Aggregate checks: Vital data will be compared against established population norms and gold standard data from Shivgarh on a monthly basis. Monthly reports will be generated by data collector to detect patterns, heaping, etc.
- Monthly appraisal of data collectors will be based on the above data quality measures.

- Independent quarterly quality audits

Statistical methods

Analysis will be done by intention-to-treat. Participants who were residing in a particular cluster at the time of enrolment into the study will be analyzed as part of that cluster.

Point estimates (summary statistics) of outcome measures for each study arm will be calculated as the mean of cluster values, giving an equal weight to each cluster.[35]

For binary outcomes (mortality, incidence, prevalence), the overall risk/rate for each cluster will be calculated. Risks/rates for each cluster will be shown, by strata and arm. A log transformation using Taylor series approximation will be applied to the risk/rate for each cluster for normalization.[35,37] The mean and SD of these log risks/rates will be used to obtain the geometric mean and associated 95% CI for the intervention arm of the study. Linear regression of the log mean risk/rate on strata and arm will be used to estimate the relative risk/rate and 95% CI associated with the intervention. The approximate variance for the mean risks/rates ratio will be obtained based on the residual mean square from a two-way analysis of variance (ANOVA) of cluster log-risk/rate on stratum and study arm. A 95% CI for the relative risk/rate will be calculated from this variance using a t-statistic.[38,39]

For continuous outcomes such as birth weight measurements, the overall mean for each cluster will be calculated, and means for each cluster will be shown by strata and arm. The arithmetic mean and SD of these mean scores/numbers and associated 95% CI for the intervention arm of the study will be calculated. Linear regression of the mean score/number on strata and arm (2-way ANOVA on intervention and strata) will be used to estimate the difference in score/number and 95% CI associated with the intervention.[39]

The results obtained in the intervention arm will be compared against the control arm. In case of any imbalance in the study arms identified post randomization; the DSMB will recommend adjustments to the analysis at its initial meeting.

Sub-analyses are planned for premature/full-term, low birth weight/normal birth weight, facility/ home births, wealth quintiles and number of visitations/emollient use (dose).

In addition to the above, cluster-level secondary per protocol analyses will be conducted to study only those babies who used oil as envisaged with their outcomes, comparing to those in control clusters.

The key definitions used are as follows:

a) Reproductive age group: While the global definition of reproductive age group is between 15 and 49 years for women, due to problems with age reporting, we will consider all women with self-reported age (or age reported by any other adult respondent in the family) above 12 years of age and not having attained menopause, as belonging to the reproductive age group.
b) Last Menstrual Period (LMP): This refers to the first date of the last menstrual period as reported by the respondent woman in reproductive age group (WRAG).
c) Pregnant woman: A woman who claims to be pregnant and whose LMP is at least 2 months prior to the enrolment date
d) Abortion (spontaneous or planned): A pregnancy that is terminated either spontaneously or through intervention, within 28 weeks of LMP.
e) Stillbirth: Post 28 weeks of gestation, a baby that does not cry, breathe or move at any time post birth (prior to 28 weeks, will be considered as abortion).
f) Livebirth: A baby that is born live, that is, it shows signs of crying, breathing or movement after birth, is considered an instance of livebirth.
g) Neonatal Death: A baby that was born live, but dies within 28 completed days from the time of birth, is a case of neonatal death.

h) Maternal Death: A woman who dies during pregnancy or within 45 completed days since delivery or abortion, irrespective of other underlying illnesses, but not due to an injury that is accidental in nature.

Evaluation of safety and reporting of adverse events

A Data Safety Monitoring Board (DSMB) has been constituted for the study. The DSMB will monitor serious adverse events, including newborn deaths, severe generalized skin rash, severe skin reaction or infection, differential hospitalization rates.

Limitations of the study

The study will test the effect of cold-pressed sunflower seed oil with accompanying directions for its use (improved massaging practices) in a population with high baseline neonatal mortality rate where massage with mustard oil in presence of high-risk skin care practices is the norm. This is largely representative of the high-mortality belt in this region, comprising of Uttar Pradesh, Bihar, Jharkhand, Orissa, Madhya Pradesh and even Bangladesh.

As we are not testing the product *alone*, therefore based on the results of the study, no comparisons may be drawn between the protective effect of the 2 oils in isolation. However, the aim of the mechanistic studies is to arrive at plausible biological pathways that may modulate the effect of the oil.

Moreover, while cold-pressed SSO has been proposed to be used as its efficacy has been proven in hospital-based studies, it is possible that some other untested locally available natural oil may have equivalent or greater protective effect than SSO. This may be a subject of smaller equivalence studies in the future, where different oils may be compared for equivalence based on potential markers identified through mechanistic studies.

As all efforts will be made to limit the difference between the intervention and control arms only to the proposed intervention, the results of this study will fill a critical evidence gap on the effectiveness of emollient application and newborn skin care as a public health intervention aimed at reducing the risk of infection and mortality in newborns.

Sustainability

This trial tests a product-based intervention of a product (cold-pressed sunflower oil) that is not currently available in the mass market, but is an important first step in understanding whether public health efforts aimed at reducing risk of newborn infections and death through emollient application and improving newborn skin care are justified. The product, therefore, cannot be made immediately available for use by communities. If results are positive, then potential channels in the private sector (including small scale industries) and public health delivery system can be explored for its production and distribution in an equitable manner.

The trial will however ensure, that the improved massage practices are sustained in the community. We have prior experience with regards to an essential newborn care intervention in Shivgarh, where our strong engagement with the community and involving community volunteers to improve the adoption of the intervention has led to improvements in care practices that have sustained over the last 10 years. We will use lessons from our past experience to guide the engagement with the local community in order to ensure sustenance of good practices.

Ethical considerations

Approvals

Ethical approval for this study will be sought from the CEL Institutional Review Board and the WHO Ethics Review Committee.

Community Consent

Prior to enrolment, community consent for the trial will be obtained from a representative group of community leaders from the entire study area.

Individual consent

At the time of enrolment, the study objective, participant involvement, risks and benefits, confidentiality issues, etc. will be explained to each respondent. An informed consent in the presence of a witness will be obtained, and participants will be informed that their participation is entirely voluntary and they are free to withdraw from the study at any point in time.

Referral of sick babies and mothers in participating communities

As part of standard operating procedures, regardless of study arms, data collectors will encourage referral of sick newborns and mothers to competent and accessible health facilities.

Confidentiality of information

All information and data collected will be de-identified at the time of analysis, reporting and distribution. Knowledge of identity of respondents will be restricted to data collectors and their supervisors.

Dissemination of results to the community

At the end of the trial, the results of the trial will be disseminated to all community stakeholders. If the trial results are positive, nauns in the control arm will also be trained in the improved massage practices.

Trial registration

The trial will be registered under the International Standard Randomised Controlled Trial Number Register, and the Clinical Trials Registry of India. In addition, a Universal Trial Number will also be obtained from the WHO International Clinical Trials Registry Platform, to uniquely identify the trial.

Conflict of Interest

The study investigators declare that they have no conflict of interest.

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