HeLTI EINSTEIN - Update added on 1 August 2025

Changes made during the course of the study:

Unblinding: In 2018, the HeLTI Research Committee (RC) sought feedback from external experts in clinical trials, epidemiology, statistics, ethics and DOHaD science about the unblinding of results to investigate interim analyses. After consideration of this feedback and extensive further discussion, the HeLTI RC had resolved to unblind at different times of the trials, to investigate interim analyses at the end of each of the four phases (preconception; pregnancy; infancy (0-2 years); and early childhood (3-5 years)). However, in order to protect the reporting of the primary outcomes, these analyses will be declared a priori as part of the analysis plan.

Intervention delivery: Due to the impact of Covid-19, and the reluctance of the potential participants to undergo physical contact and group work, we initially delivered the intervention individually to participants. However, interventions are now being delivered in both individually and in small groups, depending on participant preference.

Data collection: Baseline data collection takes place in two rounds; the first phase consists of questionnaire data mostly collected remotely using tablets and mobile phones; face-to-face collection is undertaken for those who have no access to mobile phones or are unable to answer over phones. A second round is undertaken for anthropometry and collection of biospecimens; this takes place in the field using a mobile laboratory. Where deliveries take place outside the study area when participants move to maternal homes, we are sending our field staff to collect data where feasible. Otherwise, we collect birth measurements from delivery records. Capacity for field biospecimen collection and biorepository has been enhanced with the addition of another mobile laboratory and additional freezers. We are using resources in an optimal manner to send our team outside the study area for data collection which has resulted in a significant increase especially in newborn measurements.

Progress update

Extensive formative work was completed between Sep 2018 and Feb 2020. Engagement with the local community, village leaders, government administrators and health officials was undertaken and the study was well received. Target villages (N=105) were mapped and enumerated (~37,000 households with a population of ~1,40,000); ~4500 eligible women eligible were identified. Focus group discussions (N=15) with village women, husbands, mothers/mothers-in-law, health workers, village leaders and officials were completed. Assessment of nutritional status highlighted the double burden of malnutrition in this setting. Biospecimen collection and processing protocols were standardised, and intervention modules were developed and finalised (six pre-conception and ten pregnancy and post-natal), taking into account the findings from the formative phase. However, the Covid-19 pandemic changed timelines and progress. Recruitment process for the main study commenced in February 2021. Questionnaire data is mainly being collected using remote methods (telephone and portable tablets). Intervention is being delivered using a mix of individual and group approaches. Anthropometry and biospecimen collection commenced once it was deemed Covid-safe and the community felt comfortable with physical contact.

Over 5000 participants have been recruited so far with retention of ~90%; baseline questionnaire data has been collected on ~85% while biospecimens have been collected on ~70%. Over 1400 deliveries have taken place and ~250 are currently pregnant. Of the children born, ~600 have reached age 2. We have data on over 1200 women during pregnancy. Detailed neonatal anthropometry has been carried out in ~70% newborns and DXA undertaken in ~35%. We also have data on over 650 husbands. Over 13,000 intervention sessions have been delivered to participants with intervention being initiated in

~90% of eligible participants. Biospecimens are being collected in the field using two mobile laboratory vehicles. The infrastructure for a substantial biorepository is being developed and samples are being split across three sites (Holdsworth Memorial Hospital, Mysuru Vivekananda Memorial Hospital, Saragur and CSIR-CCMB, Hyderabad) to ensure safe preservation and availability for future analyses. We have over 1,35,000 samples in our biorepository so far. We have recently commenced the collection of cord blood, placenta, newborn blood and breastmilk samples.