Improving Linear Growth of Children in Low Resource Settings through Integrated Nutrition, Health, WASH, Psychosocial Care and Support Interventions during the Pre- and Peri-conceptional Period, Pregnancy and Early Childhood - A Randomized Controlled Trial

Women and Infants Integrated Interventions for Growth Study (WINGS)

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BACKGROUND

Stunting is associated with increased child morbidity and mortality and, is also a risk factor for obesity and cardiovascular disease in later life (1). Stunting has also been linked to poor school performance that translates to reduced economic potential for the individual, and gross national product at scale (2, 3). It is quite likely that efforts to improve linear growth result in better health outcomes. Low birth weight (LBW) resulting from both prematurity and intrauterine growth retardation is a predictor of linear growth in early childhood and important risk factor for stunting, in addition to its substantial contribution to mortality (4).

Stunting in young children is associated with factors that can be categorized as modifiable and non-modifiable. Modifiable factors include maternal illness, smoking and under-nutrition in pregnancy, maternal mental and psychosocial health, preterm birth, LBW, inadequate nutrition in infancy and early childhood, repeated infections such as diarrhoea or malaria, inappropriate water quality and sanitation, and sub-optimal infant stimulation and responsive caregiving practices (5). The effects of other factors such as maternal stunting and poverty appear non-modifiable, at least in the short term.

The concept of the 'first 1000 days' highlights the critical window of opportunity between conception and 2 years of age to deliver interventions that will improve the survival, health and growth of children. Mothers living in poverty are most likely to have the risk factors of stunting described in the above paragraph. Poor nutrition during pregnancy can impair fetal growth and has been shown to be associated with preterm birth and small-for-gestation (SGA) newborns. Observational data also demonstrate a relationship between substance use in mothers, specifically alcohol and tobacco use, and maternal depression on child growth and development (6). Following birth, growth in the first two years of life is largely driven by improved infant feeding practices, including optimal breastfeeding and complementary feeding practices, and the absence of significant morbidities (7).

Most of the available studies have tested the effect of standalone interventions within the first 1000 days window on child growth and development. The tested interventions were in the domains of nutrition, family planning, physical or psychosocial health. These interventions were found to have modest effects on linear growth. It is possible that the effects are synergistic if the interventions are implemented together as a package. It would therefore, be worth evaluating a comprehensive package inclusive of all growth- and development-related interventions that can substantially improve linear growth.

Although the 1000-day period is indeed a critical window of opportunity, the state of physical and psychosocial health and nutrition of the mother at the time of conception could also influence fetal and infant growth. Under-nutrition and deficiency of micronutrients such as iron, iodine and folic acid in women at the time of conception can have substantial and devastating effects on infant health and development outcomes (8-11). Hypothyroidism, pre-existing hypertension and diabetes, and reproductive tract infections (RTI) can also affect infant survival, health and growth (12). The impact of a comprehensive package of pre- and peri-conception interventions on linear growth of children has not yet been evaluated and is not a part of most public health programs. Another important programmatic issue to bear in mind is that the current antenatal care programs start only at the time of identification of pregnancy and therefore, do not cover the entire 1000-day window. If substantiated by new evidence, addition of a pre- and peri-conception component to the existing programs would have the benefit of covering early pregnancy even before its identification by the woman and by the health system.

To summarize, there are the following important unanswered questions with regard to improving linear growth in young children in a resource-constrained setting:

- Does delivery of nutritional and non-nutritional interventions to address major causes of poor linear growth in an integrated and concurrent manner during the 1000-day window at both household and facility levels have a substantial effect on reducing LBW, preterm birth and SGA, and stunting at 2 years of age?

- Does addition of pre- and peri-conception intervention package to the interventions delivered in the 1000-day window enhance the impact on reducing LBW, preterm birth and SGA, and stunting at 2 years of age?
- Can innovation in delivery or careful tailoring of standard interventions improve acceptability by families and enhance impact?
- Does maternal height modify the effect of the intervention package on reducing stunting at 2 years of age?

The proposed study attempts to answer all these questions.

AIM

To achieve optimal growth and development in infants and children living in a resource-constrained setting in India through integrated and concurrent delivery of a package of evidence-based interventions, innovations in delivery, effective engagement and facilitation at households and facilities, and by covering the continuum from pre- and peri-conception period to early childhood. We wish to learn whether acceleration in linear growth of children of short mothers is feasible at the same rate as of mothers who are not short. It is also important to evaluate the impact of a pre- and peri-conception intervention package in women on LBW, preterm birth, SGA, early growth and development of their children.

HYPOTHESIS

i. Integrated and concurrent delivery of health, nutrition, WASH, and psychosocial care and support interventions to non-pregnant married women who want to have a child (**pre- and peri-conception intervention package**) in a resource-constrained setting will significantly reduce LBW, preterm birth and SGA, and stunting at 2 years of age compared to women not receiving this intervention package.

ii. Integrated and concurrent delivery of health, nutrition, WASH, and psychosocial care and support interventions to women during pregnancy and to their children during the first two years of life (**enhanced antenatal, postnatal and early childhood care**) in a resource-constrained setting will significantly reduce LBW, preterm birth and SGA, and stunting at 2 years of age compared to those who receive routine antenatal, postnatal and early childhood care.

iii. Integrated and concurrent delivery of health, nutrition, WASH, and psychosocial care and support interventions to women and children living in a resource-constrained setting throughout the pre- and peri-conception period, pregnancy and early childhood (**pre- and peri-conception intervention package and enhanced antenatal, postnatal and early childhood care**) will significantly reduce adverse birth outcomes and improve linear growth of children at 24 months of age compared to those who do not receive pre- and peri-conception intervention package and receive routine antenatal, postnatal and early childhood care.

iv. The effect of the above intervention packages will be similar in stunted (<150 cm) and non-stunted (≥150 cm) women. In other words, there will be no significant interaction between the effect of the intervention on growth outcomes and maternal height.

OBJECTIVES

Primary Objectives

To determine the effect of integrated and concurrent delivery of interventions to improve health, nutrition, WASH and psychosocial status:

- during pre- and peri-conception period alone (**pre- and peri-conception intervention package**)

- during pregnancy and early childhood (**enhanced antenatal, postnatal and early childhood care**) and
- throughout pre- and peri-conception period, pregnancy and early childhood (**pre- and peri-conception intervention package and enhanced antenatal, postnatal and early childhood care**)

on LBW, preterm birth and SGA, and stunting at 24 months in urban and peri-urban low-mid socioeconomic neighbourhoods in South Delhi compared to routine care.

To assess whether the effect of these interventions differs by maternal stature (<150 cm or ≥150 cm).

Secondary Objectives

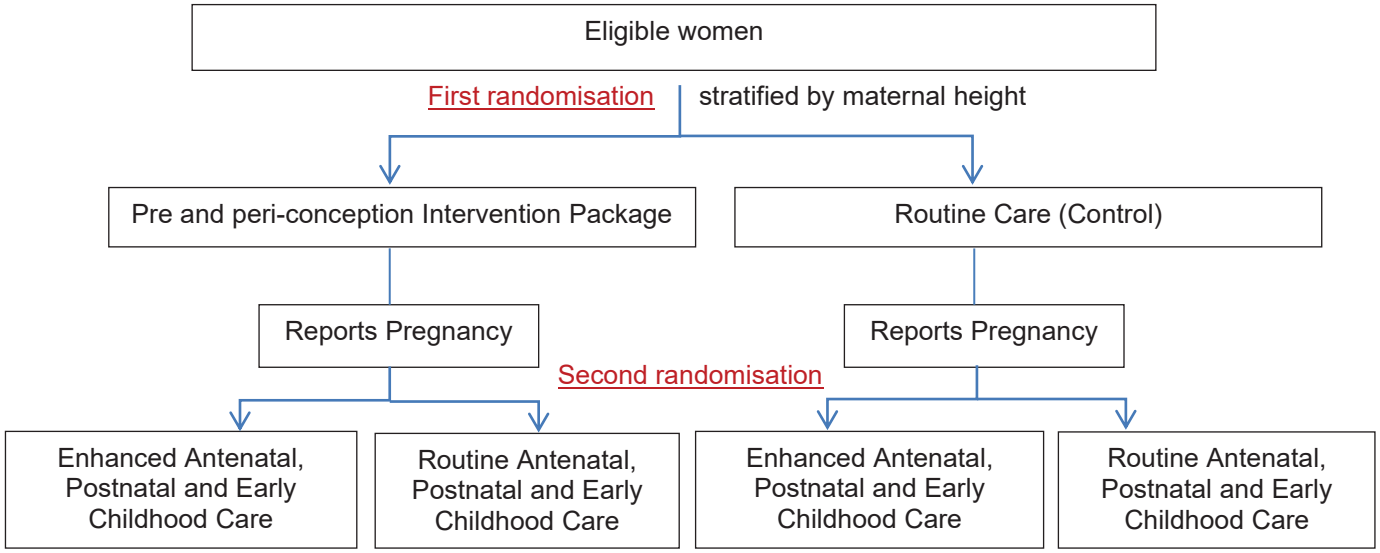
To determine the effect of the package on nutritional status, morbidity and neurodevelopment in children

To determine the effect of the package on nutritional status and morbidity in the pre- and peri-conception, pregnancy and postpartum periods in women

Study Design

An individually randomised trial with a factorial design.

Figure 1. Study design



The two randomizations will result in four groups (Group A, Group B, Group C and Group D) which will eventually receive the following

Group A	**Group B**	**Group C**	**Group D** (Control Group)
Pre- and Peri-conception Intervention Package and Enhanced Antenatal and Postnatal and Early Childhood Care	Pre- and Peri-conception Intervention Package and Routine Antenatal and Postnatal and Early Childhood Care	No Pre- and Peri-conception Intervention Package and Enhanced Antenatal and Postnatal and Early Childhood Care	No Pre- and Peri-conception Intervention Package and Routine Antenatal and Postnatal and Early Childhood Care

The study will be conducted in urban and peri-urban low-mid socioeconomic neighbourhoods of South Delhi (13).

LBW (~25%) and stunting (~40%) rates in under twos in the proposed study settings are similar to the national average (14). The maternal undernutrition (BMI <18.5 kg/m^2) rate of 22% is also similar to the national average.

For the hospital-based part of the study, the interventions will be provided at Safdarjung Hospital which is a 1600-bed multi-specialty hospital and one of the largest government tertiary care hospitals in Delhi. The Departments of Obstetrics & Gynecology and Pediatrics will support management of referrals during the pre- and peri-conception period, pregnancy and early childhood in the hospital and its outreach clinic in the study area. About 80% of the study population seeks care from this hospital for significant illnesses.

Study Participants

Married women aged 18 to 30 years wanting to have a child, living with their husbands, and those that consent for participation will be enrolled and followed up until they are confirmed to be pregnant or have completed 18 months of follow up. Once a woman is confirmed to be pregnant, she will be consented again for her and her infant's participation in the trial.

Interventions and Control Groups

The interventions in the four domains were selected if evidence was available on their impact (direct or indirect) on linear growth

	Intervention group	**Control group**
Pre-conception	**Health**: Screen and treat medical conditions known to affect fetal and infant growth, contraceptives to women who need them, bi-annual deworming **Nutrition:** Iron folic acid (IFA) supplementation, multiple micronutrients supplementation, screen and manage malnutrition and anemia, egg or milk to women with BMI <21 kg/m^2 **WASH:** Promotion of personal, menstrual and hand hygiene **Psychosocial Support:** Promote positive thinking and problem-solving skills, screen and manage depressive symptoms, substance abuse and exposure to second hand smoke An electronic monitoring system for tracking women with problems to support them for achieving intervention compliance.	Weekly IFA supplementation as part of National Iron Plus Initiative program
Pregnancy	**Health**: Minimum eight antenatal contacts, Screen and treat medical conditions, Tetanus Toxoid immunization, Calcium and vitamin D supplementation, deworming. **Nutrition:** IFA supplementation, multiple micronutrients supplementation, Provision of locally-prepared snacks to women with BMI <25 kg/m^2, milk to all women with BMI <30 kg/m^2, Weight monitoring and management for low weight gain **WASH:** Provision of water filters, soap, hand washing station, disinfectant **Psychosocial Support:** Promote positive thinking and problem-solving skills, screen and manage depressive symptoms, substance abuse and exposure to second hand smoke An electronic monitoring system for tracking women with problems to support them for achieving intervention compliance	Routine antenatal care

	Intervention group	Control group
Postnatal (Infant and children)	**Health**: Educate the mother and other family members to identify danger signs and early care seeking for illness, Counsel on timely immunisation **Nutrition: 0-6 mo:** Counselling on initiation of breastfeeding within first hour of birth and exclusive breast feeding till 6 months of age, lactation support. Growth monitoring and management of inadequate weight gain, vitamin D supplementation, Iron supplementation for very low birth weight (VLBW) infants **6-24m:** Counsel on timely initiation of complementary feeding and continuing breastfeeding till 24 months, Provide daily food supplement with 125 kcal/ 2.5 grams protein up to 12 months and and 250 kcal energy and 5 g protein from 12 to 24 months that includes 80 to 100% RDA of micronutrients , Counselling on preparing home based foods and responsive feeding, IFA supplementation **WASH:** Provision of play mat and potty **Psychosocial Support:** Counselling, demonstration and practice session for mothers and other family members on early child play and responsive care An electronic monitoring system for tracking infants with inadequate weight gain for appropriate management	Routine Postnatal and early childhood care
Mother (0-6 m postnatal period)	**Health**: Facilitate postnatal hospital visit at 6 weeks **Nutrition:** IFA, Calcium, Vitamin-D supplementation and multiple micronutrients supplementation, Daily provision of locally-prepared snacks and milk supplement **WASH:** Continue all the WASH interventions as being provided during pregnancy **Psychosocial Support:** Promote positive thinking and problem-solving skills, screen and manage depressive symptoms, substance abuse and exposure to second hand smoke An electronic monitoring system for tracking women with problems to support them for achieving intervention compliance	

The details of the interventions are provided in Annexure 1.

Women in the control group will receive routine care (http://nhm.gov.in/). The primary difference in the two groups is that delivery of care in the intervention group will be supported by the study team. All government programs are also delivered through the government clinics and the Integrated Child Development Services Scheme (https://www.icds-wcd.nic.in/) running in the area.

OUTCOMES

Primary outcomes

- Attained length at 24 months of age - length for age Z-score, proportion stunted (length for age Z-score <-2 SD)

- Mean birth weight and length (day 7 of birth), proportion LBW (birth weight < 2500 g)
- Proportion preterm birth (USG confirmed gestational age at birth of <37 completed weeks)
- Proportion SGA (birth weight less than the 10th centile for a specific completed gestational age using the Intergrowth standards)

Secondary outcomes

Children

Growth and development

- Attained length (mean LAZ) and proportion stunted at 6 and 12 months of age
- Attained weight (mean WAZ, mean WLZ) and proportion underweight and proportion wasted (based on WLZ or MUAC) at 6, 12 and 24 months
- Weight and length growth trajectories between birth and 24 months
- Mean head circumference at birth, 12 and 24 months
- Body composition at 1 month of age in a subgroup
- Caregiver reported developmental outcomes at 12 and 24 months of age
- Cognitive, language and motor scores at 24 months of age
- Mother infant bonding at 6, 12, 18 months of age by Observation of Mother-Child Interactions (OMCI) tool in a sub group

Micronutrient status

- Mean Vitamin A, D, B12, Zn, Fe, Folate concentrations and proportion deficient at 24 months of age.
- Mean haemoglobin and proportion anemic at 24 months

Inflammatory markers

- C-reactive protein
- Alpha-acid glycoprotein

Morbidity

- Severe infection in the neonatal period
- Period prevalence of diarrhea and pneumonia in 0-5 months and 6-24 months
- Hospitalizations for illness from birth to 24 months of age

Feeding practices

- Breastfeeding initiation within1 hour of birth
- Exclusive breast feeding at 1 and 5 months
- Continued breastfeeding at 12, 18 and 28 months
- Complementary feeding assessment at 9, 12, 18 and 24 months in a subgroup

Women

At the time of reporting of pregnancy or at the end of pre- and peri-conception period

- Mean BMI and proportion underweight (BMI <18.5 kg/m^2)
- Symptoms of RTI (self-reported)
- Depressive symptoms by PHQ-9 (PHQ-9 score $\geq$10)
- Birth to pregnancy interval/ marriage to pregnancy interval
- Anemia status by haemoglobin (Hb) assessment

- Micronutrient status (Vitamin A, D, B12, Zinc, Fe, Folate, Se)
- Inflammatory markers (C-reactive protein, Alpha-acid glycoprotein)
- Thyroid status by TSH assessment
- Diabetes status by HbA1C

During pregnancy

- Weight gain during pregnancy from identification to 26-28 week and identification to 35-37 weeks of pregnancy
- Symptoms of RTI (self-reported) at 35-37 weeks of gestation
- Anemia status by Hb assessment at 35-37 weeks of gestation
- Micronutrient status (Vitamin A, D, B12, Zn, Fe, Folate, Se) at 35-37 weeks of gestation
- Inflammatory markers (C-reactive protein, Alpha-acid glycoprotein)
- Birth outcomes

Postpartum

- Still births
- Mean BMI at 6 and 12 months post-partum and proportion underweight
- Depressive symptoms (by PHQ-9) at 2 and 12 months post-partum
- Anemia status by Hb assessment at 6 months post-partum
- Micronutrient status (Vitamin A, D, B12, Zn, Fe, Folate, Se) at 6 months post-partum
- Inflammatory markers (C-reactive protein, Alpha-acid glycoprotein)
- Postpartum morbidity

While the trial is ongoing, we propose to disseminate information on disease burden in women of reproductive age e.g. prevalence of non-communicable diseases (diabetes, pre-diabetes, hypothyroidism, hypertension, depression), nutritional problems (prevalence of anemia, micronutrient deficiency, malnutrition), infectious disease (RTI, tuberculosis). We will also publish family planning practices and prevalence of substance use (both smokeless and smoke tobacco, alcohol) among the women of reproductive age. This will aid policy makers and program managers in India to prioritize interventions for women in the reproductive age group.

Additional biological samples and physiological measures will be collected among subsamples of women and children to examine mechanisms by which interventions promote growth or mitigate known risk factors for impaired growth. These could include, but is not limited to, collection and analysis of stool samples for systemic or gut mucosal inflammation; or analysis of body composition. Separate proposals will be developed on these aspects.

Inclusion criteria

- Women 18-30 years of age
- Married and living with their husband with no child or 1 child and wish to have more children
- Consent to participate

We are enrolling women living with their husbands and wish to have a child. Unmarried women who are living with their partners, in Indian culture, report that they are married. We are not seeking any proof of marriage for participation in this study.

Exclusion criteria

- Moving away from the study area

- Households with no concrete roof, no toilet in the house, no water connection and no legal electricity (these households are likely to relocate).

Randomization

Randomization will be conducted twice: First: the unit of randomization will be women who meet eligibility criteria; Second: the unit of randomization will be women among those enrolled who are confirmed to be pregnant. The randomisation list will be prepared off site by a statistician not otherwise involved with the trial. Randomization will be by blocks stratified by maternal height [<150 cm (< -2 SD) and ≥150 cm (≥-2 SD)] of the WHO standards to enable assessment of the intervention effects according to maternal height.

Allocation

Participant Identification numbers will be given through a web based allocation system.

Blinding and masking

The study is not blinded. The intervention delivery teams will have limited interaction with the Outcome Ascertainment team. An attempt will be made to keep the Outcome Ascertainment team unaware of the intervention group to the extent possible.

Sample size

Assumptions

All sample size calculations are based on 90% power and 95% confidence level except for prematurity for which the power is 80%.

We have assumed minimum meaningful yet plausible effect sizes for all outcomes based on our understanding of literature.

The assumed effect sizes are larger for combined effect of pre and peri-conception intervention package, enhanced antenatal, postnatal and early childhood care group because of multiple interventions which have some evidence of individual effect.

Available literature suggests that the largest impact of a single intervention during pregnancy on mean difference of birth weight is ~50 g (0.1 SD), and reduction of LBW is~15% (15, 16). The largest impact of a single intervention during pregnancy and/or post-natal period on mean difference of attained length ~ 0.4 cm (0.1 SD) and reduction of stunting at 24 months of age ~15% (17). We have assumed at least 1.5 times higher effect size for the impact of either pre and peri-conception intervention package or enhanced antenatal, postnatal and early childhood care compared with control. We have assumed at least 2 times higher effect size for combined effect of pre and peri-conception intervention package and enhanced antenatal, postnatal and early childhood care compared to control

Effect of pre- and peri-conception intervention package alone A+B vs C+D) or Enhanced antenatal, postnatal and early childhood care alone (A+C vs B+D)

	Main effect size	**Sample size per two groups**
Linear growth at 24 months - Mean LAZ - Proportion stunted (30%)	 0.15 SD (Absolute value 0.65 cm at 24 months) 25% relative reduction	 935 772

	Main effect size	Sample size per two groups
Birth weight/birth length Proportion LBW (25%)	0.15 SD (Absolute value 75 g birth weight and 0.35 cm birth length) 25% relative reduction	935 918
Preterm birth (12%)	25% relative reduction	**2193**
SGA at birth (36%)	25% relative reduction	558

Combined effect of pre- and peri-conception intervention package and enhanced antenatal, postnatal and early childhood care (A vs D)

	Main effect size	Sample size per group
Linear growth at 24 months - Mean LAZ - Proportion stunted (30%)	 0.20 SD (Absolute value 0.80 cm at 24 months) 30% relative reduction	 527 491
Birth weight/birth length Proportion LBW (25%)	0.20 SD (Absolute value 100 g birth weight and 0.45 cm birth length) 30% relative reduction	527 624
Preterm birth (12%)	30% relative reduction	**1100**
SGA at birth (36%)	30% relative reduction	381

We aim to get 1100 live births and 600 children in each group (group A, B, C, D)

The sample size of 2400 (600 children in each group) will allow us to detect an interaction odds ratio (IOR) of ≥1.70 to 1.85 in proportion of stunted children among short mothers and proportion of stunted children among tall mothers between control (Routine care) and the full package intervention group with 80% power and 95% confidence interval.

We propose to enrol and randomize a total of 13500 eligible women (6750 in pre- and peri-conception intervention package and 6750 in control group).

The assumptions at each step are described in Annexure 2.

Once the study is ongoing, the number of women who become pregnant will be reviewed with the possibility of enrolling more women if the numbers fall short.

The DSMB will review all sample size assumptions when 50% of babies expected to be included in the study have been born, and make recommendations on sample size.

The DSMB will do a second review when 50% of babies expected to be included in the study have reached 2 years of age.

Ethical considerations

Ethical clearances will be obtained from the Ethics Committee of the Society for Applied Studies, Safdarjung Hospital, the World Health Organization and other partners, if required.

All participants will be given small gifts at enrolment and during subsequent visits. These may include items for the home and subsequently for the baby. The total cost of these items will not exceed INR 500 during any 6 month period, during the two year pre- and pre-conception period; INR 500 during pregnancy and INR 1000 over the 2 years from birth to the end of follow up.

Informed consent

A written individual informed consent will be obtained from married woman at enrolment. Husbands and other family members will be involved during the consenting process and their support would be sought. If the woman wants to keep a consent form and discuss with her family, the team will go back at a convenient time. A second consent will be taken when the woman gets pregnant. Consent will be taken from the woman for her and her child's participation in the study. Specific details of the number of visits and procedures at each visit will be explained to her. In those who are unable to read, the consent form will be read out by the worker obtaining consent. In those who are unable to sign, a thumb imprint will be taken which will be witnessed (counter signed) by an impartial literate witness. The informed consent form will be translated into simple Hindi language that can be easily read and understood.

Confidentiality

Researchers will keep all information collected private and confidential; data will be reviewed only by the immediate research team. Data at the community level will be de-identified before analysis.

STUDY TEAMS AND IMPLEMENTATION STRATEGY

Screening and Enrollment Team

Eligible women will be identified through a survey. Pairs of workers belonging to the screening and enrollment team will be allocated pockets (blocks) of the population. The team will conduct a door-to-door survey to identify eligible women (married women with one child or no child). If a woman is identified in a household, the family will be given information about the study. If the family is interested, the women will be screened for eligibility and participation into the study and a written informed consent will be taken. It will be ensured that the family members are involved during the consenting process. Prior to obtaining signatures on the consent form, questions will be asked to ascertain the understanding of women and families regarding the overall intent of the study, the two groups to which they can be allocated to (intervention and control), the duration of follow up, the number of visits and the interventions that will be delivered to the intervention group.

The pair of workers will take consent, and subsequently the weight, mid upper arm circumference and height, fill the baseline form and allocate the participant to the intervention (pre- and peri-conception) or control (routine care) group. If there are more than one eligible woman in the household, both will be enrolled and randomised to the same group. After enrollment, the intervention group women will be visited by the Health and Nutrition Team.

Women will be asked to report when they get pregnant and designated workers will keep in touch with them every month through phone calls or home visits.

Pre- and Peri-conception Period

Health and Nutrition Team (HNT)

The intervention group women will be visited by a study supervisor (Post-graduate in Social Work or Nutrition or graduates with research experience) for delivering Health, Nutrition, WASH and Psychosocial Care and Support interventions.

Activities at enrollment

Health

The supervisor will ask for symptoms of RTI, tuberculosis (TB) and history of epilepsy and measure blood pressure. A blood specimen will be taken to screen for anemia (haemoglobin), diabetes (HbA1c), thyroid disorder (TSH) and syphilis (RPR). Advice on contraception will be given to women living with husband for less than a year, having child aged less than 1 year and those with illnesses such as severe malnutrition, severe or moderate anemia, hypothyroidism, RTI/sexually transmitted infections (STI) and diabetes. A single dose of anti-helminthic will be given at enrolment

Nutrition

Women will be counselled on the benefits of an appropriate diet and on the energy, proteins, vitamins and minerals which could be obtained from a variety of locally available foods. Multiple micronutrients (40 to 80% of RDA) will be advised thrice a week. All women (Hb >12 g/dL) will be given a preparation containing iron (100 mg) and folic acid (2400 µg) and vitamin-B12 (15 µg), weekly. Women with mild to moderate anemia (Hb 8 to <12 g/dL) will be treated with IFA for 3 months. Locally-prepared snacks and egg/milk will be given to women according to their BMI (Annexure 3).

WASH

Women will be counselled on personal hygiene, menstrual hygiene and hand hygiene (Annexure 4).

Care and Support

Women will be screened for depressive symptoms using the PHQ-9 and will be managed according to the severity of depressive symptoms and presence or absence of suicidal ideation (18). A counselling module will be developed through adaptation of the WHO Thinking Healthy Module (19) for perinatal depression. Thinking Healthy uses strategies of cognitive behavior therapy (CBT) to bring about a change in the mothers negative outlook and functioning. It aims to break the cycle of unhealthy thinking (cognition), leading to unhelpful emotions and the resulting undesirable behavior. It further aims to enable a woman to feel positive about herself and ensures active self-coping skill enhancement. Apart from being a management tool for minimal depressive symptoms, we believe that adoption of the concepts of thinking Healthy by women would maximize the overall compliance to other interventions delivered. The women will be counselled against tobacco use (smoke and smokeless form) and alcohol consumption and on ways to reduce exposure to second hand smoke. Family members who reportedly smoke inside the house will be counseled to either stop smoking and if that is not possible, then to smoke outside the house or away from the vicinity of the women. Husbands will be encouraged to quit alcohol if it is a cause of perceived stress to the woman.

Follow up visits

Screening of symptoms of RTI, symptoms of TB, history of epilepsy, depressive symptoms, counselling on WASH and care will be done by the supervisor every 3 months until the women is confirmed to be pregnant or she has completed 18 months of follow up in the pre- and peri-conception period.

Blood investigations will be repeated for all women after one year of enrolment. Additionally, woman diagnosed with anemia at enrolment will be assessed for Hb level every 3 months till she becomes non-anaemic. In women diagnosed with thyroid disorders, TSH will be repeated every 2 months. Woman

diagnosed with diabetes and pre-diabetes at enrolment will be assessed for HbA1c every 3 and 6 months respectively.

Referral to infertility clinics will be facilitated for women who complete 18 months of follow up and are not pregnant but desire to get pregnant.

Participants' experiences about frequent home visits by different study teams will be ascertained in a subsample of women in the intervention group, who complete 18 months of follow up.

Referral

Women with severe anemia, diabetes, prediabetes, high blood pressure (≥140/90 mmHg on 2 separate occasions; 48 hrs apart), hypo- and hyper-thyroidism, presumptive TB, Rapid plasma reagin (RPR) positive and with symptoms of STI/RTI, epilepsy and severe undernutrition (BMI <16 kg/m^2) will be referred to the tertiary care hospital (Safdarjung Hospital). Referral will be facilitated through easier access to consultation and provision of transportation. An outreach clinic in the study area will be established with support from Safdarjung Hospital for those who are unable to visit the hospital. Those unwilling to seek care from Safdarjung Hospital will be advised to visit other hospitals in the area.

Follow up teams

Study Community Health Workers (*Sangini* – meaning "Friend")

Follow up visits will be done by study community health workers (on the lines of the government ASHA workers; http://www.nhm.gov.in/communitisation/asha/about-asha.html), called *Sangini*.

These workers will visit enrolled women at least once a week till they get pregnant or complete 18 months in the pre- and peri-conception period. The *Sangini* will promote compliance to all the Health, Nutrition, WASH and Care interventions through observed intake of medications (whenever possible) and nutrition supplements and ensure uninterrupted supplies. Compliance to the nutrition interventions will be documented for 7 days every month. Women may tend to share the snacks with young children in the household; we will provide additional supplies to these women to ensure that they have enough supplements for themselves.

The egg/milk supply will be done by workers residing in the study communities. These women will deliver eggs or milk 5 days a week to study women allocated to them in close vicinity to their place of residence. These community workers will ensure observed intake of egg or milk 5 days a week till the women's nutritional status improves.

Pregnancy

Monthly calls will be made to each woman during the pre- and peri-conception period by the Screening and Enrollment Team. When a woman reports missing two periods or a positive urine pregnancy test, a trans-abdominal ultrasonogram (USG) will be performed between 9 and 13 weeks of gestation. Once pregnancy is confirmed by USG, consent will be taken for second randomization.

Pregnant women in the intervention group will be visited by the study supervisor (Post-graduate in Nutrition, or Social Work or Graduates with similar work experience) for delivery of Health, Nutrition, WASH and Psychosocial Care and Support interventions. The study supervisors will conduct home visits at least once a month till 32 weeks of gestation, twice a month from 32 to 36 weeks of gestation and weekly thereafter till delivery.

Interventions

Pregnant women in the intervention group will be counselled on the importance of regular antenatal care, institutional delivery, danger signs in pregnancy and preparation for breastfeeding and infant care. Visits to antenatal clinics in the referral hospital (Safdarjung Hospital) will be facilitated through easier access and provision of transportation. With support from Safdarjung hospital, we will establish an outreach clinic

close to the study area for participants who are unable to go to the hospital. Pregnant women will be encouraged to comply with the investigations, treatment advised and tetanus toxoid immunization given at antenatal clinics. Post randomization, two USGs will be done at 26-28 weeks and 35-36 weeks of gestation, both in intervention and control groups. The USG will be performed in a facility run by licensed practitioners in accordance to the Prenatal Diagnostic Techniques Act 2002 [20).

Nutrition

Women will be counselled about the benefits of consuming adequate diet during pregnancy and on the energy, proteins, vitamins and minerals which could be obtained from a variety of locally available foods. The women will be advised to take IFA (100 mg elemental iron and 500 µg folic acid) and calcium (1 g of elemental calcium) and vitamin D (12.5 mcg) from 14 weeks of gestation and throughout pregnancy. Multiple micronutrients will be given throughout pregnancy. Pregnant women with BMI <25 kg/m^2 will be given locally-prepared snacks and milk throughout pregnancy. Those with BMI 25-29.99 kg/m^2 will be given only milk. Monthly weight measurements will be taken for all pregnant women.
Community workers will deliver milk to pregnant women in the areas allocated to them and will attempt to ensure its intake in their presence. Additionally, a pre-mix will be given to pregnant women with BMI <18.5 kg/m^2.

WASH

Women will be counselled on personal and hand hygiene. Water filters will be provided and counselling on use of safe drinking water, its storage and handling will be provided. Food grade plastic bottles will be provided for storage of water. If not already available, a handwashing station will be set up inside the home; monthly soap and disinfectant supplies will also be provided.

Care and Support

Women will be counselled to promote positive thinking and problem solving skills, based on Thinking Healthy Module developed by WHO (19). Women will be screened for depressive symptoms using PHQ-9, four times during pregnancy. Those with depressive symptoms (PHQ-9 ≥10 and/or suicidal ideation) will be referred. The women will be counselled against tobacco use (smoke and smokeless form) and alcohol consumption and on ways to reduce exposure to second hand smoke. Family members who reportedly smoke inside the house will be counselled to either stop smoking and if that is not possible, then to smoke outside the house or away from the vicinity of the women. Husbands will be encouraged to quit alcohol if it is a cause of perceived stress to the woman.

Postnatal and Early Childhood Period

Once discharged from the hospital, the intervention group women and child will be visited by study ASHA like worker (*Prerna*) for delivering Health, Nutrition, WASH and Care interventions.

Postnatal Interventions: Mother (0 -6 months)

Health

All women will be encouraged to go for postnatal visits as per WHO recommendations on Postnatal Care (21).

Nutrition

Mothers will be provided locally-prepared snacks and milk and IFA, calcium, vitamin D and multiple micronutrients for the first 6 months during the postnatal period.

The milk will be delivered 5 days a week by community workers who will try and observe its intake.

Care and support

Mothers will be counselled to promote positive thinking and problem solving skills, based on Thinking Healthy Module developed by WHO (19). A PHQ-2 screener will be administered to recently delivered

mothers, within a week of delivery (22). The intent is to identify mothers with low mood who need psychosocial support very early in the postnatal period. Subsequently, mothers will be screened for depressive symptoms using PHQ-9, thrice during first six months i.e. at infant ages 1, 3 and 6 months. Those with depressive symptoms (PHQ-9 ≥10 and/or suicidal ideation) will be referred to hospitals. The women will be counselled against tobacco use (smoke and smokeless form) and alcohol consumption and on ways to reduce exposure to second hand smoke. Family members who reportedly smoke inside the house will be counselled to either stop smoking and if that is not possible, then to smoke outside the house or away from the vicinity of the women. Husbands will be encouraged to quit alcohol if it is a cause of perceived stress to the woman.

Childhood Interventions

0-6 months

All infants will be visited by *Prerna* worker in the first 6 months of life with following frequencies: within 24 hours of birth/discharge, day 3, day 7, day 14, day 28 and monthly from month 2 to 6. Additional visits will be made for preterm and LBW infants.

Health and Nutrition

The mother and other family members will be trained to identify danger signs in infants and seek early care for illnesses. In families who report danger signs in their infants, referral to Safdarjung Hospital will be facilitated. Timely immunization will be advised.

Mothers will be counselled to breastfeed exclusively for first 6 months. The *Prerna* worker trained in lactational counselling will conduct home visits to promote essential new born care as per the national home-based neonatal care guidelines (23). For preterm infants additional visits for lactation counselling will be done in first three months. Micronutrients supplementation will be advised for LBW and VLBW infants as per WHO recommendations (24). Weights will be taken monthly. Infants with inadequate weight gain (<15th centile as per WHO weight velocity/month), morbidities and with mothers reporting breastfeeding problems will be managed accordingly. Management of severe acute malnutrition during first 6 months will be done at health facilities (25).

Care and support

One of the essential components of the care and support domain is the early child development interventions. *Prerna* workers will counsel the mother and family members on ways to interact and communicate with the child, starting from birth. Father's involvement in caring for the child will be encouraged. At specific points of time i.e. at 3 and 6 months of age, the team will assess key developmental milestones. Infants who could not attain age specific milestones will be referred to trained psychologists. The interventions for early child development have been adapted using Care for Child Development Manual, prepared by UNICEF and WHO (26).

6-24 months

All children will be visited monthly by *Prerna* workers.

Health

The mother and other family members will be trained to identify danger signs in infants and advised to seek care for illnesses early. Referral to Safdarjung Hospital will be facilitated for infants with any danger signs. All mothers will be advised about timely immunization. Six-monthly deworming will be done from 12 months of age for all children.

Nutrition

Mothers will be counselled to continue breastfeeding till the child is 24 months of age. Counselling on complementary feeding will include initiation at 6 months through a visit 1-2 week prior to infant age 6

months. Demonstrations will be conducted on how to prepare foods at home which can be fed easily to the child and ways to encourage the infant to eat more. Around 50% of extra energy needed in addition to breast milk will be supplemented through a balanced protein energy supplement that is culturally acceptable. Daily iron supplementation will be given as per WHO recommendations (27). Growth monitoring (weight and length monthly up to 12 months and thereafter 3 monthly up to 24 months) will be done by the *Prerna* workers. Children with severe acute malnutrition (weight for length Z-score <-3 SD) will be managed at facilities (25). Children with moderate malnutrition (weight for length Z-score < -3 to -2 SD) will be done at home by providing counselling on preparing augmented food.

Care and Support

Mothers will be counselled to promote positive thinking and problem solving skills, based on Thinking Healthy Module developed by WHO (19). Mothers will be screened for depressive symptoms using PHQ-9 at 9, 12 and 18 months of child age. Those with depressive symptoms (PHQ-9 ≥10 and/or suicidal ideation) will be referred. Mothers will be demonstrated and practice sessions will be arranged at each home visits on early child play, stimulation and responsive care based on UNICEF child play and stimulation guidelines (26). Mothers will be counselled on early child development. If any delayed development identified, referral will be facilitated.

WASH in the postnatal period (0 to 24 months)

Interventions will continue on

- Safe drinking water (from filters provided during pregnancy)
- Counselling on hand hygiene of both mother and child
- Counselling on safe disposal of faeces, use of diapers and appropriate storage of diapers before disposal.
- Provision of potties for the children at ~8 to 9 months of age for defecation.
- Clean play area through provision of play mats at 6 months of age.
- Counselling on food hygiene, appropriate and hygienic ways of food preparation and storage of food.

Program Learning Team

The Program Learning Team comprising of at least 2 persons will measure compliance through observations and interviews, and will also gauge the performance of the study against pre-defined process indicators. This team will also explore reasons for non-compliance, and identify barriers and enablers through in-depth interviews. This feedback will be given to the intervention delivery teams.

Outcomes and Their Ascertainment

An independent Outcome Ascertainment Team will visit at pre-decided intervals to document outcomes: primary and secondary.

Collection and Storage of Blood Samples

Blood samples will be collected from women and children at the following time points:

- ~10 ml at enrolment from women in the intervention group for screening of VDRL, anemia, thyroid, diabetes, and nutritional factors.
- ~10 ml when pregnancy is reported from women both in intervention and control groups for anemia, screening of metabolic disorders and to assess infectious and nutritional factors. We will also attempt to take blood specimens from women who do not become pregnant during the study period

- 10 ml blood from all women at in the third trimester of the pregnancy in both groups to assess anemia and micronutrient status
- 10 ml from all mothers 6 months postpartum in both groups to assess anemia and to assess infectious and nutritional factors
- 5 ml from all children at 24 months of age in both groups for micronutrient assays.

The samples will be centrifuged and stored in a -80°C deep freezer until analysis.

Assessment of body composition

The isotope dilution technique using deuterium oxide (2H2O) will be used to estimate infant body composition, as per International Atomic Energy Agency (IAEA) guidelines (28). Infants will be given a single oral dose (0.2 g/kg) of 2H2O at Day-28. The subsequent enrichment of 2H2O in body water will be analysed in infant saliva samples, collected before and 2 and 3 hours after the oral 2H2O dose. The samples will be collected in a cool box and will be transported within 4-6 hours to SAS lab for storage. The saliva samples will be stored at -20 degree Celsius until analysis, as per IAEA guidelines. Appropriate labelling and storage of the samples will be re-checked. The samples will be shipped (on dry ice), once or twice a year, to St. John's Research Institute (SJRI), Bangalore for analysis. Enrichment of deuterium in infant saliva samples will be assessed by Fourier transform infrared (FTIR) spectrophotometry (28).

LABORATORY INVESTIGATIONS

All laboratory investigations will be done by an accredited commercial laboratory and at referral hospitals.

The samples will be stored in the "Clinical and Research Laboratories" set up at the SAS office at the field site in Devli and which is accessible only to the Laboratory Managers. The samples will be stored for 5 years after the completion of study period and may be used for sub-studies and hypothesis related to nutrition and growth outcomes for research purposes only.

ULTRASONOGRAPHY FOR ASSESSMENT OF PREMATURITY AND FETAL GROWTH RESTRICTION

A trans-abdominal USG will be scheduled between 9 and 13 weeks of gestation as per reported LMP. If woman reports positive urine pregnancy test after 13 weeks of gestation as per reported LMP, a trans-abdominal USG will be scheduled as early as possible. This scan will be used to estimate gestational age (GA). Gestational age will be calculated by fetal crown-rump length (CRL). If CRL> 95 mm, femur length and head circumference will be used to assess gestational age (29). Subsequent USG examination for pregnant women will be to look for fetal growth restriction.

Following the initial scan, women will have at least 2 scheduled scan at 26-28 weeks and 35-36 weeks of gestation.

Essential measurements

At all examinations after the initial dating scan, the following measurements will be taken:

1. Biparietal diameter (BPD)
2. Occipito-Frontal Diameter (OFD)
3. Head circumference (HC) using the ellipse facility
4. Abdominal circumference (AC) using the ellipse facility
5. Femur length (FL)

Essential documentation

At all examination after the initial dating scan, the following will be documented:

1. Fetal presentation (cephalic, breech, transverse, oblique)

2. Placental localization (fundal, high anterior, high posterior, high right lateral, high left lateral, low anterior, low posterior, low right lateral, low left lateral).

3. Amniotic fluid volume (polyhydramnios, increased, normal, reduced, oligohydramnios, anhydramnios).

The study team will facilitate all the USGs both for intervention and control groups at the designated USG centres. All the radiologists are trained in INTERGRWOTH-21 standards. All the USGs will be done for outcome assessment purpose and will not be a part of the intervention. For the pregnant women in the intervention group, the study team will facilitate antenatal care in Safdarjung Hospital. The USG reports will be made available to doctors at ANC clinic to support quality care. For the control group, the study team will counsel the pregnant women to take the USG report while going for antenatal care.

Methods of Assessment

Three measurements will be taken for each fetal biometric variable: CRL, BPD, OFD, FL, HC and AC, with the woman in the lateral recumbent position. In addition, the amniotic fluid index, to assess amniotic fluid volume, and the fetal presentation and placental position will be documented. All images will be stored in a hard drive. The radiologist performing the scan will be blinded to group allocation of the pregnant women. Images from 10% of all study participants will be randomly selected and sent for external review.

TRAINING AND STANDARDIZATION OF STUDY TEAMS

Prior to study initiation, different categories of staff will be trained in the overall study objectives, strategy and in their individual job responsibilities.

The Screening and Enrolment Team will be trained in identification of eligible women, process of enrolment, obtaining written informed consent and taking anthropometric measurements (weight and height).

Health and Nutrition team will be trained to administer questionnaires to ascertain suspected morbidities and to facilitate referral to Safdarjung Hospital. The research team at Safdarjung Hospital will be trained in management of morbidities according to research protocols and government guidelines. The team will also be trained in delivering nutrition interventions at home and counselling. This team will also be trained to administer PHQ-9 and counselling on menstrual and personal hygiene.
Sanginis will be trained in assessment of compliance and counselling participants who do not comply with the nutrition interventions.
The Pregnancy Intervention Delivery Team will be trained in delivery of nutrition, care and WASH interventions at home and counselling. This team will also be trained in assessment of compliance and counselling those who are non-compliant.
The *Prerna* team will be trained in lactational counselling, delivery of nutrition, care and WASH interventions at home and counselling. This team will also be trained in assessment of compliance and counselling those who are non-compliant.
The independent Outcome Ascertainment Team will be trained in measurement of all outcomes such as anthropometry measurements, administering tools for measuring symptoms of depression (PHQ-9) and development and ascertaining morbidity in pre- and peri-conception period, pregnancy and childhood.
The team will undergo inter- and intra-observer standardization exercises for anthropometry measurements (weight and length/height).
The Program Learning Team will be responsible for helping us understand the barriers to adoption of different interventions.

The Postnatal team will be trained in delivery of nutrition, care and WASH interventions at home and counselling.

The Data management team will be trained in designing and maintaining databases, assuring quality of data collected and preparing tables and summaries for review.

All study staff (except the support staff) will also receive training in Good Clinical Practice (GCP) guidelines.

DATA MANAGEMENT AND ANALYSIS

The Data Management Centre (DMC) will be set up in the field office. Most of the data will be collected electronically. We have a secure, access controlled cloud server where the database will be stored. All data transferred from tablets or net books will have 256 bit secure socket layer encryption during transmission to maintain confidentiality of the data. The database can only be accessed by administrator who has the rights for the same. All data will be stored for up to 7 years after the completion of the study as mandated by national guidelines.

Range and logical checks will be incorporated into the entered data. Real time data will be transferred to a local server at the DMC. Checks across forms and logical error checks will be run at the DMC. Queries generated will be given to study team for resolution and corrections incorporated.

Data analysis

The data from this study will answer four research questions using the following analysis strategy appropriate for the factorial design:

Question 1: What is the impact of pre- and peri-conception intervention package on birth outcomes and attained length at 24 months of age?

Analysis strategy: Infants of women randomized to receive pre- and peri-conception intervention package (groups A+B) will be compared with the group randomized not to receive this package (groups C+D). Birth outcomes of groups A+B that will be compared with those of groups C+D are mean birth weight and length, and proportion preterm birth, SGA and LBW. Attained length for age and proportion stunted at 24 months of age will be compared between the groups.

Question 1a: What is the impact of pre- and peri-conception intervention package on the health and nutritional status of women at the time that they get pregnant?

Analysis strategy: Women randomized to receive pre- and peri-conception intervention package (groups A+B) will be compared with the group randomized not to receive this package (groups C+D). Outcomes will be compared between groups A+B and groups C+D at the time of confirmation of pregnancy and will include nutritional status based on BMI, anemia status, hypothyroid status, diabetes status, presence of depressive symptoms, and presence of symptoms of RTI.

Question 2: What is the impact of enhanced antenatal, postnatal and early childhood care on birth outcomes and attained length at 24 months of age?

Analysis strategy: Infants of women randomized to receive enhanced antenatal, postnatal and early childhood care (groups A+C) will be compared with the group randomized to receive routine antenatal, postnatal and early childhood care (groups B+D). Birth outcomes of groups A+C that will be compared with those of groups B+D are mean birth weight and length, and proportion preterm birth, SGA and LBW. Attained length for age and proportion stunted at 24 months of age will be compared between the groups.

Question 3: What is the combined impact of pre- and peri-conception intervention package and enhanced antenatal, postnatal and early childhood care on birth outcomes and attained length at 24 months of age?

Analysis strategy: Infants of women randomized to receive both pre- and peri-conception interventions and enhanced antenatal, postnatal and early childhood care (group A) will be compared with the control

group randomized to receive routine care (group D). Birth outcomes of group A that will be compared with those of group D are mean birth weight and length, and proportion preterm birth, SGA and LBW. Attained length for age and proportion stunted at 24 months of age will be compared between groups A and D.

For binary outcomes such as LBW, preterm birth, SGA at birth and stunted at 2 years of age, generalized linear models (GLMs) of the binomial family with a log-link function will be used to calculate the effect size (Relative Risk and 95% CIs). For continuous outcomes such as birth weight, birth length and length for age at 2 years of age, GLMs of the Gaussian family will be used to calculate the effect size (difference in means and 95% CIs).

If there are important baseline differences between groups, potential confounders will be added to the model to adjust the effect of the intervention on primary outcomes. Maternal height categorized as <150 cm and ≥150 cm will be included as interaction term in models evaluating the effect of interventions on primary outcomes to learn whether the intervention effect is modified by maternal stature.

The effect of interventions on secondary outcomes will be assessed using the same models as for primary outcomes.

Data custody and confidentiality

The data coordinator and the data manager will have access to the data. The custody of the data will be with the data coordinator. All the computers and screens will be password protected. All personnel in the data management centre will be given user access authorization. All staff will undergo training as per ICH-GCP guidelines before initiation of the study to ensure that they are aware of the confidentiality and protection of data. Trial-related monitoring, audits and Ethics Review Committee inspections will be permitted by providing direct access to source data and documents.

Data Safety Monitoring Committee

The Data Safety Monitoring Committee (DSMC), will be a technical body constituted by the WHO will be responsible for monitoring and assessing the safety of the trial. The DSMC will be composed of five members - an epidemiologist, a statistician and a clinician/social scientist. All the members will be independent of the study team. The study investigators will be available for the DSMC meeting, whenever required. A written declaration of no conflict of interest will be obtained from each member of the DSMC. Meetings will occur at the pre-decided frequency (tentatively twice a year) during the data collection phase to review data. Decision on the interim analysis, stopping rules will be taken by the committee.

All serious adverse events, including deaths, in enrolled participants will be reported to World Health Organization for further communication to the DSMB, in addition to local ethics committee.

Oversight and monitoring

The World Health Organization, Geneva and Biotechnology Industry Research Assistance Council (BIRAC), Department of Biotechnology, Government of India will be responsible for oversight of the study.

ROLE OF PARTNERS

CHRD-SAS

The investigators from CHRD-SAS will be responsible for overall study implementation. They will facilitate referral to hospital for women and children who need it as per protocol during pre- and peri-conception, pregnancy and early childhood period. They will also be responsible for all data collection, specimen collection, transportation and storage.

Safdarjung Hospital

The collaborators from Safdarjung Hospital will support management of referrals during the pre and peri-conception period, pregnancy and early childhood. In the pre and peri-conception period, this will be

achieved through the peri-conception clinic. and for antenatal care and delivery and subsequently through early childhood through the routine services. Provision of quality care to the study participants in a standard and efficient manner is deeply embedded in the study and will be ensured through a coordinated effort by all study partners in Departments of Obstetrics & Gynecology, Medicine and Pediatrics supported by link physicians from CHRD-SAS.

Hamdard Institute of Medical Sciences & Research (HIMSR)

HIMSR has National Accreditation Board for Hospitals (NABH) accredited radiology department, empanelled by Central Government Health Scheme (CGHS), Government of India. The department is part of Medical Council of India recognized Hamdard Institute of Medical Sciences and Research, Teaching Hospital. The department has 24 x 7 radiology services that include facilities of MRI, CT, USG, Doppler, Fluoroscopy, Digital radiography, OPG and image guided intervention. It also has fully digitalised - PACS enabled reporting and is PC & PNDT compliant. The department has dedicated GE Voluson for Obstetrics and Gynaecology work with linear, curvilinear, Transvaginal and 3D-4D probes with DICOM networking.

Qualified and experienced radiologists are available full time and will serve as one of the collaborators.

TIMELINES

Activity	**Timelines**
Preparatory Phase (6 months)	1-6 months
Recruitment Phase (24 months)	7-30 months
Peri-conception Intervention period (18 months)	7-36 months
Pregnancy Phase (9 months after the last woman gets pregnant)	8-45 months
Postnatal period and Follow up (till 24 months)	17-69 months

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ANNEXURE 1. DETAILS OF INTERVENTIONS

Pre- and Peri-conception

Intervention	Control
HEALTH Screen and treat medical conditions known to affect fetal and infant growth i.e. i.e. reproductive tract infections, syndromic approach (RTI), symptoms of tuberculosis (TB), Hypertension, Diabetes (HbA1c ≥6.5%) and Pre-diabetes (HbA1c 5.7%-6.4%), Hypo-thyroidism (thyroid-stimulating hormone (TSH) >5.5 mIU/ml or TSH 4.01 to 5.5 mIU/l and anti-TPO Ab positive) and Hyper thyroidism (<0.4 mIU/ml) Treat those with medical conditions Provision of contraception to women living with husband for <1 year, having child <1 year, severe malnutrition, severe to moderate anemia, hypothyroidism, RTI/STI and diabetes Bi-annual deworming	Weekly IFA supplementation as part of the National Iron plus Initiative Program
NUTRITION Weekly IFA supplementation (Iron 100 mg and folic acid 2400 mcg) to all All women screened for malnutrition and anemia All women given multiple micronutrients thrice weekly(Vitamin A, C, B12, B6, B1, B2, Zinc, Selenium, Copper, Magnesium, Iodine), IFA prophylaxis and nutritional counselling **Malnutrition** BMI <16 kg/m^2: Refer to hospital and food supplementation (1000 kcal,20-22 protein/ day) and egg or milk BMI 16 to 18.40 kg/m^2: Food supplement (500 kcal) and egg or milk (70 kcal, 6 g protein)BMI 18.5 to 20.99 kg/m^2: Egg or milk (70 kcal, 6 g protein) 6 days a week Monthly weight assessment for those with BMI <18.5 kg/m^2 and management of inadequate weight gain **Anemia** Severe anemia (Hb <8 g/dL): Hospital treatment Mild to moderate anemia (Hb 8 to 11.99 g/dL): IFA treatment	
WASH Promotion of personal, menstrual and hand hygiene	
PSYCHOSOCIAL SUPPORT Screen all for depressive symptoms using PHQ9. Counselling by study psychologist if PHQ score ≥10. Referral to psychiatrist if PHQ-9 score ≥15 and/or presence of suicidal ideation Screen for substance abuse and exposure to second hand smoke and alcohol use in husbands and counsel Promotion of positive thinking and problem-solving skills for all . Electronic monitoring system for tracking women with problems to support them for achieving intervention compliance.	

Monitor all above interventions every 3 months until corrected or pregnant

Pregnancy

Intervention Group	Control Group
HEALTH Minimum 8 ANC contacts for all In addition to hospital based ANC clinics increase in coverage achieved by Free, High quality, Outpatient clinic within community with laboratory services, and use of electronic records to increase follow up Screening and treat for medical conditions: HIV, VDRL, syndromic STI/RTI, syndromic TB, HbsAg, hypo- and hyper-thyroidism at first contact Urine R/E, M/E and asymptomatic bacteriuria by urine culture four times Gestational diabetes by oral glucose tolerance test thrice Pregnancy induced hypertension (blood pressure and urine protein at four times) Anemia (Hb) four times Increased quality of screening and treatment achieved by home based follow up, increased time per visit guided by individual electronic digital data record of continuity of follow up Tetanus Toxoid immunization for all Calcium and vitamin D supplementation daily starting from second trimester throughout pregnancy, for all Anti-helminthic drug (Albendazole 400mg) at 20 weeks	Routine antenatal care
NUTRITION Counselling IFA supplementation daily starting from second trimester throughout pregnancy for all Multiple micronutrients (Vitamin A, C, B12, B6, B1, B2, Zinc, Selenium, Copper, Magnesium, Iodine) daily throughout pregnancy Daily locally-prepared snacks and support for women with BMI <25 kg/m^2 at the time of second randomization Second trimester: 280 kcal, 8 g protein (milk and snack) Third trimester: 470 kcal, 27 g protein (milk and snack) Milk Supplement for pregnant women with BMI <30 kg/m^2 at the time of second randomization Weight monitoring at each month for all; management of inadequate weight gain (IWG) according to Institute of Medicine's guidelines through provision of additional snacks (500 kcal, 20 g protein) Additional snack (500 kcal, 20 g protein) for pregnant women with BMI <18.5 kg/m^2 at R2 throughout pregnancy	
WASH Provision of hardware (water filters and plastic bottles soap, hand washing station, disinfectant) and counselling	

PSYCHOSOCIAL SUPPORT Screen all for depressive symptoms, substance abuse, exposure to second hand smoke and alcohol use in husbands and counsel Promotion of positive thinking and problem-solving skills for all; Thinking Healthy, World Health Organization Counselling by study psychologist if PHQ score ≥10. Referral to psychiatrist if PHQ-9 score ≥15 and/or presence of suicidal ideation Electronic monitoring system for tracking women with problems to support them for achieving intervention compliance.	

0-6 months (Infants)

Intervention group	**Control Group**
NUTRITION **For all infants** Initiation of breastfeeding within the first hour of birth Early lactation counselling for all mothers to prevent problems in BF in the first month after birth. Breastfeeding problem resolution anytime during the first 6 months Counsel on Exclusive breast feeding till 6 months of age and special Emphasis on the exclusivity of breastfeeding from 3 up to 6 months of age. **Growth monitoring and management of inadequate weight gain (IWG)** Weight measurement at age day 14 and thereafter monthly to identify Inadequate Weight Gain (IWG) for all Term infants. [IWG defined as <15th centile as per WHO MGRS growth velocity, i.e. weight gain < 20 grams /day between ages Day 14 to 2 months; weight gain < 15 g/d for months 3 and 4; weigh gain <10 g/d for months 5 and 6)] Intensified lactation support to all infants with IWG and thorough clinical examination to rule out possible causes for the same. Facility based management of IWG by senior paediatrician at SJH after 15 days of continued efforts for lactational support and no medical cause is identified which may cause IWG. Additional support for LBW babies and Preterm babies even if not LBW Additional breastfeeding support by additional Lactation Counselling through home visits in the first three months (biweekly in first month, weekly in second and third month, monthly from fourth to sixth month) Offer expressed breastmilk feeding only for preterm babies after they breastfeed Extended hospital support (through assessment of feeding, growth and investigations within 4-6 weeks after birth) after discharge and ensuring that the advice given at the facility is followed at home Support kangaroo mother care at home Vitamin D 400 IU daily for all infants up to 6 months	Routine postnatal and early childhood care

Iron supplementation at 2 weeks for VLBW and at 6 weeks for LBW An electronic monitoring system for tracking infants with inadequate weight gain for appropriate management	
HEALTH Educating the mother and other family members to identify danger signs and early care seeking for illness. Facilitate referral to health facility for infants with any danger signs or illness requiring facility based management. Counsel on timely immunisation	
PSYCHOSOCIAL CARE Counselling, demonstration and practice sessions for mothers at each home visit on Early child play and responsive care. Identify of delayed development and timely referral for further management	

0-6 months (Mother)

Intervention group	**Control Group**
HEALTH Facilitate mandatory Postnatal hospital visit at 6 weeks.	Routine postnatal and early childhood care
NUTRITION **For all** Daily locally-prepared snacks and milk, 600 kcal, 20g protein) for first 6 months of postnatal period. IFA, Calcium and vitamin D supplementation daily for first 6 months of postnatal period Multiple micronutrients (Vitamin A, C, B12, B6, B1, B2, Zinc, Selenium, Copper, Magnesium, Iodine) daily for first 6 months of postnatal period	
WASH Continuation of all the WASH interventions as being provided during pregnancy (Water filters and plastic bottles soap, hand washing station, disinfectant) and counselling on handwashing and hygiene practices (bathing the infant regularly, using clean clothes for the infant, keeping the infant's surroundings clean, safe disposal of infant's feces, and handwashing before handling the baby).	
PSYCHOSOCIAL CARE Promotion of positive thinking and problem-solving skills for all; Thinking Healthy, World Health Organization Screening for all mothers for depressive symptoms and management Counselling by study psychologist if PHQ score ≥10. Referral to psychiatrist if PHQ-9 score ≥15 and/or presence of suicidal ideation Ascertainment of Substance abuse and exposure to second hand smoke and counsel against	

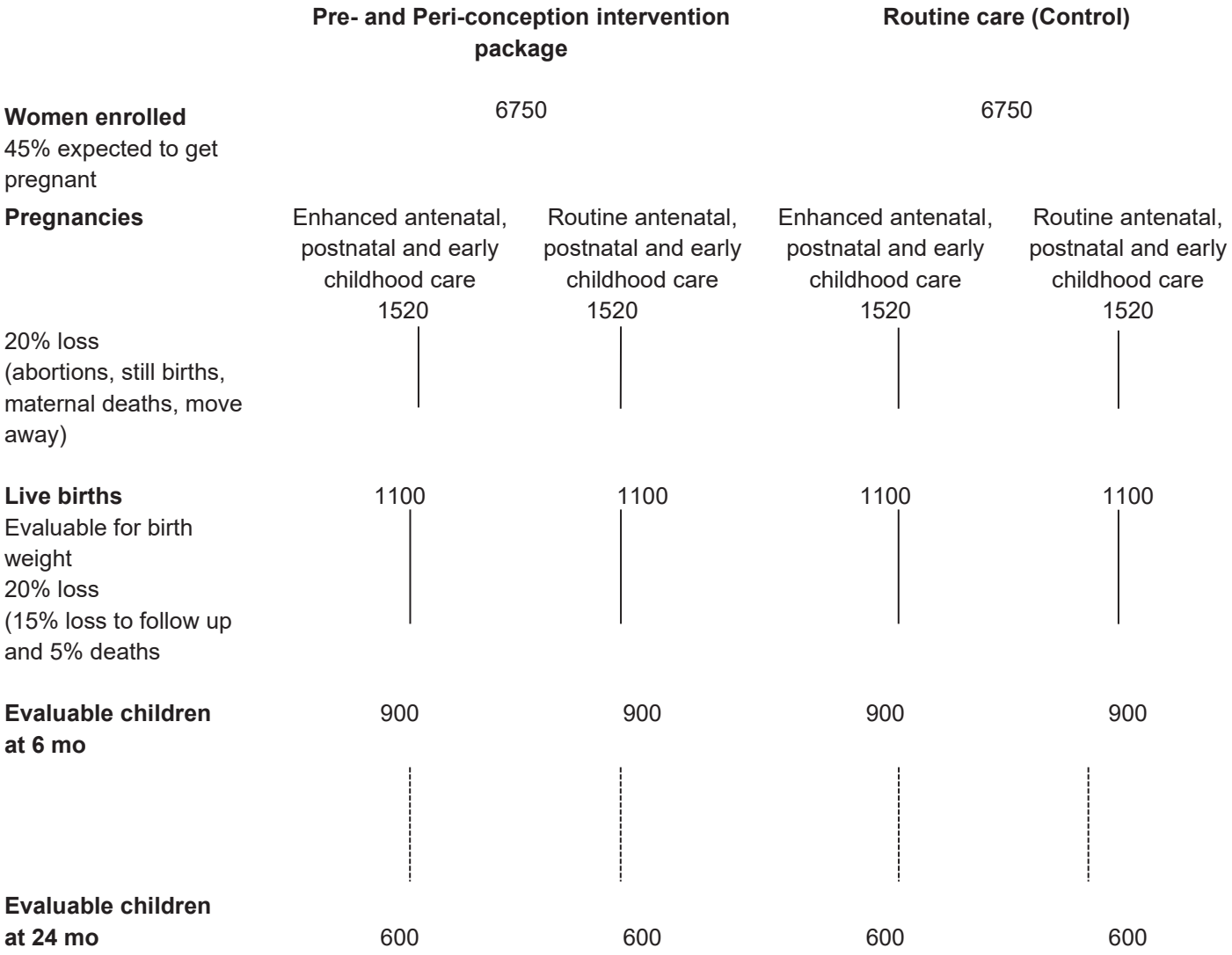
their use. Electronic monitoring system for tracking women with problems to support them for achieving intervention compliance.	

6-24 months (Children)

Intervention group	Control
NUTRITION Effective counselling on initiation of complementary feeding by preparing the mother and family 1- 2 weeks prior 6 months of infants age Initiation of Complementary feeding at 6 months of age and teaching the mother by demonstrating on how to prepare foods at home which can be fed easily to the child 6 months onwards. Provide daily food supplement with 125 kcal/ 2.5 grams protein upto 12 months and and 250 kcal energy and 5 g protein from 12 to 24 months that includes 80 to 100% RDA of micronutrients . Counselling on intake of home-based foods. Counselling and demonstration of responsive feeding to mother and family members IFA supplementation up to 2 years Lactational counselling for supporting continued BF after 6 months Growth monitoring (weight and length monthly up to 24 months) to identify faltering and refer to facility for management. Home based management of Moderate Acute Malnutrition (MAM) by providing counselling on preparing augmented home based foods. Facilitating facility based management of Severe Acute Malnutrition (SAM). An electronic monitoring system for tracking infants with inadequate weight gain for appropriate management	Routine postnatal and early childhood care
HEALTH Educate the mother and other family members to identify danger signs and early care seeking and facilitate medical management. Counselling on feeding the child during and after illness. Counsel on timely Immunization Provide Albendazole (200 mg) for deworming starting 12 months of age and 6 monthly up to 24 months of age.	
WASH Continuation of all the WASH interventions as being provided during pregnancy (Water filters and plastic bottles soap, hand washing station, disinfectant) and counselling on hygiene practices (safe preparation, storage and feeding of the child utilising clean utensils and clean water for cooking and drinking). Clean play area for children (play mat) Safe disposal of child's faeces (potty)	

PSYCHOSOCIAL CARE **CHILDREN** Counselling on early child development Demonstration and practice session for mother at each home visit on Early child play and responsive care. Identify of delayed development and timely referral for further management **MOTHERS** Promotion of positive thinking and problem-solving skills for all; Thinking Healthy, World Health Organization Screening for all mothers for depressive symptoms and management Counselling by study psychologist if PHQ score ≥10. Referral to psychiatrist if PHQ-9 score ≥15 and/or presence of suicidal ideation Electronic monitoring system for tracking women with problems to support them for achieving intervention compliance.	

ANNEXURE 2



We propose to enrol and randomize a total of 13500 eligible women (6750 in the pre- and peri-conception intervention package group and 6750 in routine care group).

ANNEXURE 3
Locally-prepared snacks and egg/milk) to be given to women according to their BMI

Based on a woman's BMI, the following be given:

BMI 18.5-20.99 kg/m^2: High protein food (egg or milk based or product with high quality animal protein)

BMI 16-18.49 kg/m^2: High protein food and an additional 500 kcal/day (assuming ~30% deficit of energy requirement and 12 to 14 g protein/day)

BMI <16 kg/m^2: High protein food and an additional 1000 kcal/day (assuming 50% deficit of energy requirement and 20-22 g protein per day)

BMI ≥23 kg/m^2: Counseling on optimal diet and increased physical activity

Weight of women in the intervention group will be measured three monthly.

ANNEXURE 4

Counselling on personal hygiene, menstrual hygiene and hand hygiene

The focus of WASH interventions will be on counselling to bring about behaviour change.

In the pre- and peri-conception period, the interventions will comprise of counselling and giving required information without provision of any WASH hardware. The emphasis during this phase will be on prevention of RTIs through counselling on personal hygiene (bathing, washing of private parts in both women and men, washing of undergarments), menstrual hygiene (information on low cost sanitary pads, safe disposal of used pads) and hand hygiene (clipping of nails, keeping nails clean, use of soap and water or sanitizer to clean hands, critical points for hand washing).

Counselling on menstrual hygiene, personal hygiene and hand washing will be done every 3 months until they are confirmed to be pregnant or have completed 18 months of follow up in the pre-and peri-conception period.