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Protocol for a cluster randomised trial evaluating a multi-faceted intervention starting preconceptionally - Early Interventions to Support Trajectories for Healthy Life in India (EINSTEIN). A Healthy Life Trajectories Initiative (HeLTI) Study.

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Protocol for a cluster randomised trial evaluating a multi-faceted intervention starting preconceptionally - Early Interventions to Support Trajectories for Healthy Life in India (EINSTEIN). A Healthy Life Trajectories Initiative (HeLTI) Study.

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Key words: Developmental origins of health and disease (DOHaD), Multi-faceted intervention; Pre-conceptional intervention; Non-communicable diseases; India

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ABSTRACT

Introduction: The Healthy Life Trajectories Initiative (HeLTI) is an international consortium comprising four harmonised but independently powered trials to evaluate whether an integrated intervention starting pre-conceptionally will reduce non-communicable disease risk in their children. This paper describes the protocol of the India study.

Methods and analysis: The study set in rural Mysore will recruit ~6000 married women over the age of 18 years. The village-based cluster randomised design has three arms (pre-conception, pregnancy and control; 35 villages per arm). The longitudinal multi-faceted intervention package will be delivered by community health workers and comprise: a) measures to optimise nutrition; b) a group parenting programme integrated with cognitive behavior therapy; c) a lifestyle behavior change intervention to support women to achieve a diverse diet, exclusive breastfeeding for the first 6 months, timely introduction of diverse and nutritious infant weaning foods, and adopt appropriate hygiene measures; and d) the reduction of environmental pollution focusing on indoor air pollution and toxin avoidance.

The primary outcome is adiposity in children at age 5 years, measured by fat mass index. We will report on a host of intermediate and process outcomes. We will collect a range of biospecimens including blood, urine, stool, and saliva from the mothers, as well as umbilical cord blood, placenta and specimens from the offspring.

An intention-to-treat analysis will be adopted to assess the effect of interventions on outcomes. We will also undertake process and economic evaluations to determine scalability and public health translation.

Ethics and dissemination: The study has been approved by the institutional ethics committee of the lead institute. Findings will be published in peer-reviewed journals. We will interact with policy makers at local, national and international agencies to enable translation. We will also share the findings with the participants and local community through community meetings, newsletters and local radio.

Trial registration: To be registered with CTRI and ISRCTN

Keywords: Non-communicable disease; Developmental Origins of Health and Disease; Pre-conceptional intervention; Childhood adiposity; Child development, Healthy Life Trajectory Initiative (HeLTI)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study will evaluate, for the first time in India, whether a multi-faceted intervention starting pre-conceptionally and continuing through pregnancy, infancy and early childhood reduces risk factors for non-communicable disease in the offspring. The design will also allow assessment of the relative benefits and costs of starting the intervention pre-conceptionally versus starting in pregnancy, in addition to standard care.
- The study builds upon 35 years of local work which has resulted in strong community engagement and rapport.
- Process and economic evaluations will help in scalability while the use of local community workers will aid translation; the choice of a setting which is undergoing socio-economic transition has major public health implications.
- Given the long-term nature of the study, unblinding of selected outcomes will occur at the end of each phase to enable interim mechanistic analyses and thereby maximise the study potential.
- Due to the study design, effectiveness of individual components of the intervention cannot be evaluated.

INTRODUCTION

Non-communicable diseases (NCDs) which include cardiovascular disease (CVD), type 2 diabetes and depression are major causes of death and disability globally[1,2] and are rising rapidly in low- and middle-income countries (LMICs) [1–3]. The rising burden of cardiometabolic disease in LMICs is accompanied by a growing recognition of the burden of mental health disorders. Depression is the leading neuropsychiatric cause of disease burden globally and in LMICs[4], and by 2020 it is projected to be the second leading cause of burden of disease[5].

In India, an estimated 65 million people have diabetes and a further 77 million are pre-diabetic, making it one of the diabetes epicentres of the world[6,7]. Unchecked, the population with diabetes is expected to reach 109 million by 2035[6]. A review showed that 13% of young people aged 1-16 years in India experience mental health disorders[8]. In later life, ~3.7 million people over 60 years of age have dementia; this number is expected to double by 2030 and triple by 2050[9]. These chronic diseases have significant economic implications; the treatment and related costs amount to INR 19914 (US$398) and INR 43285 ($865) per person per year for diabetes[10] and dementia[11], respectively.

The developmental origins of health and disease (DOHaD) hypothesis suggests that adversity during early life influences adult NCD risk[12,13]. DOHaD research suggests that NCD risk is influenced not only by exposure to the well-known 'load' factors such as adult obesity and physical inactivity, but also by the 'capacity' of key metabolic tissues, which is acquired during early development[14]. It is now well established that low birth weight (LBW), poor infant nutrition, and rapid childhood weight gain and obesity are risk factors for poor health trajectories and development of NCDs in later life[15,16].

Undernutrition (including widespread micronutrient deficiencies) remains a significant problem in India. In children under 5, the prevalence of stunting is ~35%; wasting ~17%; underweight ~33%, and anaemia ~41%[17]. In women aged 15-49 years, 23% are underweight (body mass index, BMI<18.5 kg/m^2) while ~53% are anaemic[18]. These factors are reflected in a high prevalence of LBW (<2500g) in ~21% of the 26 million babies born in India each year[19]. Rates of obesity in children and adults are also increasing in India; it is estimated that ~12% of children and ~21% of women of reproductive age are overweight or obese (adult BMI>25 kg/m^2)[18].

Application of DOHaD principles therefore offers a novel approach to tackling NCDs by delivering interventions in an integrated manner across the lifecourse: in adolescent or young women to ensure they approach pregnancy in optimum health; in pregnant women to ensure a healthy pregnancy and safe delivery; and in infancy and childhood to prevent excessive childhood adiposity and promote child development.

The Healthy Life Trajectories Initiative

In this context, the Healthy Life Trajectories Initiative (HeLTI) was launched as a joint initiative between the Canadian Institute of Health Research, the Department of Biotechnology of India, the South African Medical Research Council, the National Science Foundation of China and the World Health Organisation. This programme follows a DOHaD approach, focusing on reducing the long-term risk of NCDs through interventions that target the interaction between environmental factors and genes during pre-conception, conception, fetal life, infancy and early childhood. The HeLTI programme comprises four separate but harmonised randomised controlled trials in Mysore (India), Shanghai (China), Soweto (South Africa), and two provinces in Canada. The HeLTI interventions are multi-faceted; the rationale is that previous single intervention trials (e.g. multiple micronutrient supplementation) have shown only modest benefits for pregnancy and child outcomes and that multiple interventions are needed to create impact in populations with multiple environmental and social disadvantages. Previous trials have usually started after

confirmation of pregnancy, in the late first trimester, and have therefore missed the important peri-conceptional and early pregnancy processes of epigenetic change, placentation and organogenesis; starting pre-conceptionally will address these issues. The long-term view is unique, with all funders intending to support for 10 years so that the impact of the interventions not only on pregnancy outcomes, but also on cardiometabolic and neurodevelopmental outcomes in the children can be assessed.

The HeLTI consortium has a collective governance structure for the management of the trials. The two co-lead PIs of each of the four HeLTI trials form an over-arching Research Committee (RC), with rotating chairpersons, responsible for overall project management and oversight, liaising with working groups and reporting to the HeLTI Council (comprising representatives from all the funders and a WHO secretariat). Working groups, including investigators from all countries chaired by one of the lead PIs, develop harmonised protocols, covering biospecimens, data collection, interventions, cohort management and retention, and data management. Each country project team has a Steering Committee, comprising the two PIs and selected co-PIs, which deals with day to day operations and reports to the RC, as well as liaising with participating institutions and community representatives. The four HeLTI trials have a common Data Monitoring and Safety Committee comprising independent international experts, with representation from the four countries involved. The WHO will monitor the trial conduct.

The India Study

We report the protocol for the Indian study, Early Interventions to Support Trajectories for Healthy Life in India (EINSTEIN) in this paper. Research by our group has shown that part of the increased NCD risk in Indians comes from changes in fetal body composition. The undernourished Indian newborn is typically light and thin (average birth weight 2.7kg) and has a low lean body mass, but is disproportionately adipose (the 'thin-fat' Indian)[20,21]. This phenotype persists through childhood and into adult life, and is associated with diabetes and CVD at relatively low levels of obesity. The effects of early life undernutrition are exacerbated by poor weight gain in infancy and rapid childhood weight gain even in the absence of obesity[22].

We have specifically chosen a rural population where obesity is currently uncommon, but undernutrition is common. This population is representative of a large section of the Indian population where economic transition has started and is likely to benefit most from interventions to improve early development (capacity) as well as those that reduce the post-natal obesogenic effects of transition (load).

METHODS AND ANALYSIS

Our overarching aim is to investigate whether an integrated intervention starting pre-conceptionally and continuing at appropriate points across the lifecourse (pregnancy, infancy and childhood) will reduce childhood adiposity and the risk for NCDs as well as improve measures of child neurodevelopment.

Patient and public involvement

We undertook extensive community engagement and formative work over a period of ~18 months with the local community which included face-to-face meetings and focus group discussions. This work helped to finalise our intervention package and delivery methods, and dissemination plans.

Subjects

Our proposed study will be set in rural Mysore, in HD Kote and Saragur Taluks about 50 km from Mysore city in southern India. The population is characterised by subsistence farming, poor nutritional status, low levels of literacy particularly among women, and limited access to specialist health services. Approximately 25% of women are underweight, 19% are overweight, and 45% are anaemic[23]. Less than 60% of infants are exclusively breast fed for

6 months[24]. Over 60% of children under five are anaemic and less than two-thirds are fully immunised[23,24]. The prevalence of both stunting and underweight in children under five is ~38%[24]. Sanitation and hygiene facilities are limited and toilets are mostly shared. The local area receives potable water from taps, most commonly from shared taps situated in streets. Borewells are also a common source of water. The population is relatively stable, minimizing loss to follow up. Signs of transition are evident; village shops sell high-energy, high-salt, high-sugar snacks and drinks which are mainly consumed by children and young people. Better transport links have increased access to nearby towns and cities, allowing people to seek employment in small/cottage industries.

We have selected 105 villages based on population size (from ~250 in the area) around our main field site, the Vivekananda Memorial Hospital (VMH) in Saragur, and will allocate 35 villages to each group, using a standard computerised randomisation programme. We will include women who are over the age of 18, married, have no children or one child, and are planning to have a child within the next two years. We will particularly focus on newly married women, who have a high likelihood of pregnancy within a year.

Study design

The study is a community-based, cluster-randomised intervention with three arms (preconception, pregnancy and control), with individual villages forming the basis for the cluster. Women in all three arms will be recruited together, pre-conceptionally for baseline measurements. The longitudinal multi-faceted intervention will be delivered by trained community health workers (CHWs), which will allow future scalability.

All participants will receive iron and folic acid tablets during pregnancy as per Indian guidelines. Calcium is routinely prescribed in pregnancy by many obstetricians. We will not interfere with routine care provided by the women's obstetricians. We will liaise with local doctors to ensure that they are aware of the study and the supplements their patients are taking, so that the women do not receive 'excess' micronutrients. All women will also receive menstrual hygiene advice and will be provided with a supply of menstrual pads to promote appropriate hygiene practices.

Intervention details

Group 1 (Preconception arm):

Micronutrient supplementation: Women will receive daily micronutrient supplement tablets from recruitment preconceptionally, throughout pregnancy and during breast feeding. Given the high likelihood of multiple deficiencies, the composition will be based on the WHO/UNICEF/UNU international multiple micronutrient preparation (UNIMMAP).

Lifestyle behavior change support: Women will receive support from CHWs trained in Healthy Conversation Skills (HCS), in group settings. The principles of the group work are in Appendix 1. HCS is a communication technique developed at the University of Southampton by our wider team for use by health workers to support behaviour change in socio-economically disadvantaged women[25]. This technique has been translated to LMIC settings; in a recent feasibility study involving our group in South Africa, community health workers have been successfully trained in HCS to support young women to improve their diets and lifestyles. The group work emphasises the role of increasing self-efficacy in promoting behaviour change. It is based on the understanding that providing participants with knowledge alone is not sufficient to change their behaviour unless they are also motivated and empowered to change. The aim will be to promote a diverse diet, achieve a normal body weight, and achieve an adequate intake of micronutrients before and during pregnancy, and while breastfeeding. CHWs will provide support postnatally to encourage exclusive breast feeding for the first 6 months and the timely introduction of diverse and nutritious infant weaning foods. Women will be educated about the importance of using safe water for feeding their infants after six months, and advised to use boiled and cooled water. They will receive support to ensure that their infants are fully vaccinated, and that they adopt appropriate hygiene measures, particularly hand washing after using the toilet, changing 'nappies', and before

preparing food, eating and feeding their infants. During the pre-conception stage, the group work will be held at approximately monthly intervals. There will be six modules, with the first module serving as an introductory and general health module. This will be delivered first to all women in the arm. The other five modules will be delivered cyclically and address diet, physical activity and sleep, environmental exposure and hygiene, mental health, and preparing for pregnancy.

Group parenting and cognitive behaviour intervention (Learning Through Play Plus {LTP Plus}): LTP Plus is a group parenting programme, integrated with a cognitive behaviour therapy intervention (Thinking Healthy Programme) designed to address perinatal depression and improve child development in LMIC settings[26,27]. It is a manual assisted, low-literacy, potentially sustainable programme whose activities enhance children's development. It simultaneously promotes attachment security through building parents' ability to be sensitive to their children's cues, and be actively involved in their children's development. These sessions will be delivered in phases which will not only match the woman's pace, but also the gestational period antenatally and the infant's developmental stages postnatally. This two-pronged psychosocial participatory group intervention will help mothers to cope with stress, reduce depression and provide information and strategies that they need to nurture their children's health and development. This will consist of a total of ten sessions, three during pregnancy and seven postnatally. LTP Plus uses a standardized manual and the material will be delivered by CHWs.

Avoiding environmental pollution: We will provide advice and information on avoidance of environmental pollutants particularly indoor smoke (cooking and smoking). We will facilitate LPG (liquefied petroleum gas) connections actively through a recently introduced government scheme which provides subsidized stoves and fuel. We will also address exposure to, and safe handling of pesticides.

Group 2 (Pregnancy arm):
Women in this group will receive the same package of interventions described above, but starting only after they become pregnant, which, in practice, will mean late in the first trimester. Last menstrual period dates will be monitored monthly and women will be offered a urine pregnancy test when they report missing two consecutive periods.

Group 3 (Control arm):
Women in this group will receive an enhanced standard of care. In addition to encouraging vaccinations (two doses of tetanus toxoid) during pregnancy, provision of 100 tablets of iron and folate, and promoting institutional delivery, they will have a similar number of contact sessions with CHWs untrained in our behaviour change and parenting interventions. They will receive standard advice on healthy lifestyle during pregnancy and postnatally, supported by information leaflets (mainly pictorial and using simple language); these will include advice on breastfeeding, immunizations, and infant weaning foods.

Outcomes and assessments
The primary outcome at age 5 years in the children (across all HeLTI cohorts) is adiposity as measured by fat mass index (fat mass/height^2), using DXA (dual x-ray absorptiometry). Other key outcomes at 5-6 years in the children include:

- Overweight and obesity (OWO) as assessed by BMI and indicators of body composition and distribution (waist circumference, skinfold thickness)
- Glucose metabolism as measured by fasting venous plasma glucose concentration
- Resting systolic blood pressure
- Child development as assessed using modified Kaufman battery, validated for Indian settings.

Baseline data on all participants as well as data throughout the study at intervals will be collected

(Table 1). Additional phenotypic data will be collected in a subset (ranging between 50-200 individuals per arm, depending on the assessment). We will also collect

Sample size and power

All the HeLTI studies have calculated their sample size using a minimum power of 80% at 5% significance level to detect a 0.25 standard deviation (SD) difference in offspring fat mass index at 5 years of age between intervention and control groups. We intend to recruit ~6000 initially at baseline. We anticipate 50% will become pregnant within two years (based on data from our formative work). Allowing a 5% pregnancy loss and 20% drop out/loss to follow-up rate, we will have ~750 children in each arm available for follow up to assess our primary outcome (~22 per per village). Assuming an intra-cluster correlation of 0.03, this gives ~95% power to detect a 0.25 SD difference in fat mass between the intervention and control groups and ~80% power to detect sex differences. If pregnancy rates are lower than expected, we will undertake a second round of recruitment at the end of the first year.

Data analysis

As the main outcomes for the study are fat mass index, OWO rate, resting blood pressure, fasting glucose and neurodevelopmental outcomes at age 5 years, and as most children will achieve these ages only in cycle 2 (5-10 years of project), analyses at the end of cycle 1 (0-5 years of project) will explore the effects of the intervention on child anthropometric measures (at birth and serially) and neurodevelopmental outcomes. We will also assess effects on maternal anthropometry, mental health, behavioural risk factors for adiposity/obesity and glycemia. Process indicators including recruitment, retention, and indicators of programme delivery in the intervention group/s will also be determined.

An intention-to-treat analysis will be used for the key outcomes, based on all viable pregnancies. Analysts will be blinded to the study groups. Unblinding will occur after analysis or on the advice of the independent Data Monitoring Committee. We will use mixed models with a cluster-specific approach and robust error estimators adjusted for prespecified potential risk factors related to individual clusters and subjects (such as, locality and level of care, maternal age, parity, pregnancy complications, smoking, and socioeconomic status). First, standard data screening/cleaning procedures will be conducted including the extent and pattern of missing data. We will assess the comparability at randomization of the treatment groups using descriptive analyses. The distribution of modifiable risk factors for childhood obesity, poor cardiometabolic and neurodevelopmental outcomes at baseline, and their changes over time will be assessed according to study group. For women in the intervention groups, we will evaluate the number of scheduled intervention visits, and compliance with micronutrient supplements and attendance at group sessions.

At the end of the 1st cycle of the project, we expect the youngest children to be 1 year of age. We will evaluate the impact of the intervention on all indicators of potential risk factors including weight-for-length at 1 year, birthweight and proportions of SGA/LGA, head and abdominal circumferences at birth and 1 year of age, as well as on indicators of perinatal morbidity/mortality. We will also assess the impact of the intervention on maternal gestational weight gain, the proportion meeting international gestational weight gain guidelines, breastfeeding status as well as on maternal diet and physical activity in the preconception and pregnancy periods.

At 5 years of age in the children, we will assess the effect of the intervention on fat mass index (the primary outcome). Other anthropometric outcomes to be assessed at this time include OWO, BMI and centiles and adiposity (skinfold thickness, arm circumference). We will also assess the effect of the intervention on glucose metabolism, blood pressure and neurodevelopmental outcomes.

Mixed models with random intercept/slope effects and fixed effects (for the intervention) will

be used to estimate the intervention effect. Due to possible heterogeneity of effects for key outcomes according to the time of initiation of the intervention (e.g. preconception versus pregnancy) we will conduct a subgroup analysis stratifying by this variable, testing for heterogeneity. For a 'per-protocol' analysis, we will categorize clusters as high or low according to the compliance with implementation of the intervention. Sensitivity analyses will be performed to assess the influence of losses to follow-up. We will use data on all participants (i.e. with viable pregnancies at inclusion) through multiple imputation.

Economic evaluation: We will undertake cost-effectiveness analysis, from a healthcare payer perspective. We will collect data related to healthcare resource use during the study, including costs of the intervention, CHWs' time, and healthcare use during pregnancy, delivery and infant/child care. Unit costs will be estimated using the activity-based costing method. Our measure of effectiveness will be based on our primary outcome; we will estimate the relative cost-effectiveness of the pre-conception strategy, pregnancy strategy and standard care; an incremental analysis will be conducted comparing the three strategies.

Process evaluation: Evaluation will focus on implementation, mechanisms of impact, and context. Assessment of implementation will focus on determining what is delivered and how delivery is achieved. We will measure fidelity of intervention delivery by observing CHWs in their contacts with intervention group participants, focusing on their use of HCS and LTP Plus and the competencies they demonstrate. We will also observe the contact between CHWs and control participants to record the nature of interactions. We will monitor intervention dose by recording the frequency and duration of contact between participants and CHWs. To understand the mechanisms through which the intervention brings about change in our specified outcomes, we will assess the acceptability of the intervention, and women's experiences of contact with CHWs using interviews and focus groups. In assessing context, we will aim to identify any factor that might act as a barrier or facilitator to intervention implementation or effects. This will include local and national policy, local service configuration and provision, socio-demographic and environmental factors within the villages taking part in the trial, and consultation with key stakeholders. We will also survey non-respondents and those who drop out to gain an understanding of why they did not consent to take part in the study or dropped out during the course of the trial.

Expected outcomes:
The study will provide robust evidence whether an integrated multi-faceted intervention starting pre-conceptionally and continuing through pregnancy and postnatally reduces risk factors for NCD in the offspring. The use of culturally-appropriate interventions will allow scalability if successful. The process and economic evaluations will aid in assessment of translation potential. We will also be able to assess the relative costs and benefits of starting interventions pre-conceptionally versus starting in pregnancy. The study will generate extensive data and build a biorepository which can be used by other researchers within India and elsewhere.

ETHICS AND DISSEMINATION

Patient and public involvement
We undertook extensive community engagement and formative work over a period of ~18 months with the local community which included face-to-face meetings and focus group discussions. This work helped to finalise our intervention package and delivery methods, and dissemination plans.

Recruitment of participants
The study has been approved by the CSI Holdsworth Memorial Hospital Ethics Committee, (Ref CSIHMH/ERU2019/1). Any protocol modifications will be reported to the committee and

approval will be sought for any significant amendments. Community engagement is key to the success of our programme and we have engaged with the community leaders, village elders and local groups, particularly women's self-help groups. We held community engagement meetings at village level to explain the study and clarify any queries people may have. VMH is also actively engaged with local women's self-help groups; we will interact with them throughout the project to not only provide updates of the project, but also to incorporate their feedback into the conduct of the study.

The families will be given verbal information initially followed by written information in Kannada (local language). The participants will be encouraged to ask questions before obtaining written consent. It will be made clear that they are free to withdraw at any time from the study.

Anonymity and/or confidentiality

Every precaution will be taken to respect the privacy of the women and the confidentiality of their information. We follow research governance practice in accordance with Indian and international guidelines. All data are coded and anonymised before analysis. Strict confidentiality is maintained throughout; hard copy data are stored in locked filing cabinets and in locked rooms, with limited access. Digital data are stored on password-protected encrypted computers, with access only by authorised members of the research team. Biological samples are stored in locked freezers in a secure facility.

Potential risks/harm to participants in the study

None of the interventions or investigations present risks to the participants. Micronutrient supplements have been previously used in community trials and are recommended in the Lancet series on Maternal and Child Nutrition[28] and in the 2015 Cochrane Review on micronutrient supplementation in pregnancy[29]. While we do not expect any adverse effects due to the supplements, the participants will be monitored for adverse events. The LTP Plus programme has been used previously in various LMIC settings and has been shown to reduce maternal depression; there have been no reported adverse outcomes. HCS have also been used previously in community settings without any adverse outcomes. Serious adverse events will be investigated by a medical doctor and reported to the PI and local Co-PIs. Reports will also be submitted to the local institutional ethics committee and the sponsor. Data on adverse events will also be submitted to the independent Data Monitoring Committee. All tests are done under medical supervision and appropriate referral arrangements are in place for issues requiring medical attention.

Dissemination

Participants will receive reports of the relevant physical and biological measurements. If there are any abnormal results, participants will be referred to appropriate medical specialists in VMH for further management and advice.

To maximise the scientific impact, we will engage with the scientific community by presenting our work at major national and international conferences, and by publishing in high-quality peer-reviewed journals, ensuring open access. We will engage with other research groups working on maternal and child health, and develop collaborative opportunities even beyond the duration of the project. Our data will be available to the scientific community after we publish our main findings.

We also will interact with policy makers at local, national and international health agencies, and governments to enable translation of our findings into policy. Members of our collaborative group are linked into national and international policy advisory groups including local, state and national governmental committees in India and Canada, the WHO and Unicef, and we will ensure relevant findings are disseminated through these groups to influence policy. We have met with local health and government officials in the district

councils to discuss the public health importance of our study. Their support will be invaluable in future translation. Research findings will be translated into project summaries and policy briefs that capture the major findings and suggest practical policy changes, based on the evidence provided by the project. Recommendations to policy makers will also focus on cost-effectiveness. These documents will be published in English as well as local languages.

The results have implications for all mothers and children, and we will engage with our communities, the wider public, and the mass media. VMH runs a radio station and we will use broadcasts to engage with the local community and provide information and updates. We will explain the relevance of our research to our participants and feedback important results to them through six-monthly newsletters and also by community meetings on an annual basis. We will also publicise the study on our institutional websites and use mass media to ensure that our research findings reach a wide public audience.

In summary, our study will determine whether a longitudinal integrated intervention starting pre-conceptionally improves cardiometabolic and neurodevelopmental outcomes in the next generation. The results will have significant public health implications which can be generalised to other similar settings. The range of biospecimens being collected will allow us to understand causal mechanisms.

Table 1: List of assessments to be carried out at various time points

Mothers	**Baseline**
Physical health	Anthropometry: weight, height; Body composition: Bioimpedance, skinfolds (subset), DXA (subset), stable isotope (subset); Blood pressure: Digital sphygmomanometer
Biospecimen	Blood sample: Plasma, serum, DNA, RNA (subset)
Questionnaires	Diet: Food frequency questionnaire (FFQ), 24-hour food recall, diet diversity and food security questionnaires; Physical activity: Global Physical Activity Questionnaire (GPAQ); Sleep: Pittsburgh Sleep Quality Index (PSQI); General Self Efficacy Scale (GSES); Generalised Anxiety Disorder-7 (GAD-7); Patient Health Questionnaire -9 (PHQ-9); Adverse Childhood Experience (ACE) questionnaire Sociodemography; Socioeconomic status (Standard of Living Index; SLI); Medical/ treatment/drug history; Smoking and alcohol history
	Pregnancy
Physical health	Anthropometry: weight; Body composition: Bioimpedance, stable isotope (subset); Blood pressure: Digital sphygmomanometer
Biospecimen	Blood: Oral glucose tolerance test (OGTT), plasma, serum, DNA, RNA (subset); Urine; Saliva (subset)
Questionnaires	FFQ, 24-hour food recall, diet diversity and food security; GPAQ; PSQI; GSES; GAD-7; Edinburgh Postnatal Depression Scale (EPDS); Social Provision Scale; Breast-feeding Self-efficacy Scale; Perceived Stress Scale Sociodemography; Socioeconomic status (SLI); Medical/ treatment/drug history; Smoking and alcohol history
	Delivery
	Weight; Stool/rectal swab (subset); Delivery details
	Serial postnatal follow-up (up to 60 months)
Physical health	Anthropometry: Weight; Body composition: DXA (subset), stable isotope (subset); Blood pressure: Digital sphygmomanometer; OGTT; blood samples
Biospecimen	Blood: plasma, serum, DNA, RNA (subset), OGTT
Questionnaires	FFQ; 24-hour food recall, diet diversity and food security; GPAQ; PSQI; GSES; GAD-7; EPDS; PHQ-9; Social Provision Scale; Breast-feeding Self efficacy Scale; Perceived Stress Scale; Parenting Stress Index; Sociodemography; Socioeconomic status (SLI); Medical/ treatment/drug history; Smoking and alcohol history

Fathers	Index pregnancy
	Anthropometry: Weight, height; Body composition: Bioimpedance, DXA (subset); Blood pressure: Digital sphygmomanometer Blood: Plasma, serum, DNA, RNA (subset), saliva (subset) FFQ; 24-hour food recall, diet diversity and food security; GPAQ; PSQI; PHQ-9 Sociodemography, Socioeconomic status (SLI); Medical/ treatment/drug history; Smoking and alcohol history
Child	**Birth**
	Anthropometry: Weight, length, head/arm/abdomen/chest circumference, skinfolds DXA, Cord blood; Placenta; Umbilical cord; Meconium
	Birth to 12 months
	Anthropometry: Weight, length, circumferences; Body composition: DXA, stable isotope (subset) Feeding history; Vaccination history; Medical/treatment/drug history Stool
	Serial postnatal follow-up (major follow-up at 24 and 60 months)
	Anthropometry: Weight, length/height, circumferences; Body composition: DXA, Blood pressure; Blood samples (heel prick at 24 months and venous sample at 60 months): Plasma, serum, DNA, RNA, glycaemia Feeding history; Sleep Questionnaire; Ages and stages questionnaire; Neuro-cognitive developmental tools: Developmental Assessment *Scale* for Indian Infants (DASII) at 24 months; modified Kaufmann Battery at 60 months; Executive function assessment tools; Physical activity (questionnaire and accelerometry); Screen time questionnaire; General health assessment; Vaccination history; Medical/treatment/drug history

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Authors' contributions: All named authors were involved in study design and protocol development. KK, GVK, KGS, MPP, CHDF, PS, DS and SGM wrote the first draft of the manuscript. All authors critically reviewed the manuscript and approved the final version.

Competing interests statement: None of the authors declare any conflict of interest. The HeLTI Council of funders and WHO have required all Principal Investigators to complete annual Declarations of Interest and to commit to having no direct or indirect relations with the tobacco, arms and infant food industries during the course of the study.

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Data sharing and access: Data sharing and access arrangements are included in the overall HeLTI governance document. The HeLTI consortium is in the process of establishing a Data Access Portal though which investigators can view and request access to data/biospecimens within individual HeLTI country or multiple country datasets. Data access will follow country-specific guidelines and is expected to require submission of a detailed research plan (including study rationale, hypothesis, analytic methodologies and funding support to complete the study/analyses). Once the study is completed the researchers will be required to submit all analytical and derived data with metadata to be integrated into the HeLTI country datasets, so that it is available to other researchers.

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Appendix 1: HeLTI India (EINSTEIN) Group Work Principles

Intended beneficiaries: Community health workers (CHWs), based at Vivekananda Memorial Hospital will facilitate a series of peer group discussion and learning sessions among all women enrolled into the intervention arms, i.e. the pre-conception and pregnancy arms (and no peer support intervention will be delivered to participants allocated to the control arm).

Components: The peer support "package" will consist of:

(i) Sequential facilitation of 6 pre-conceptional, 5 pregnancy and 5 post-natal timed & targeted content modules by trained CHWs
(ii) Training and refresher sessions for CHWs on Healthy conversation skills (HCS), Learning Through Play Plus (LTP+), and intervention modules facilitation, conducted by trainers from CSI Holdsworth Memorial Hospital
(iii) Regular observation and supportive supervision of CHWs by Quality Control teams and field supervisors/manager.

Materials: Participants each receive a *personalized* pictorial resource/work booklet for the whole set of sessions.

CHW will receive resource guides, attendance and delivery log sheets, and reflection report guides.

Logistics: Peer support groups will be convened in groups of up to 10-12, for delivery each month. In each intervention village/cluster there may be ~30 women enrolled at the beginning, so there will be multiple peer groups per cluster. As more women are enrolled as they become eligible, the groups may increase. After enrollment and baseline data collection (including biospecimens), the initial session will be conducted by a CHW ~2-4 weeks later. Subsequent sessions will be conducted on a "timed and targeted" schedule roughly every month.

Rationale and process of development: The primary topics and specific content mix for each session were developed based on:

- Context of existing services, if any
- Alignment with key goals of the study
- Prioritisation of women's health needs, identified with key stakeholder consultations
- Feedback from initial community engagements (e.g. people recognised that they won't benefit and changes won't be immediate, will benefit future generations, their children).

Spillover chances/potential contamination, although possible, are considered low because of the:

- Individual nature of intervention (including booklet materials being personalized)
- Peers support group discussions are private, small-scale

- Limited social media.

Guiding principles of the peer group sessions:

- Empowering women participants
- Timed and targeted to reproductive stage
- Integrated with HCS approach
- Topical mix packaged unconventionally, but coherently from participant perspectives
- Ground-truthed, using formative research and pre-testing
- Cyclicity, with short enough amplitude for re-exposure during a pregnancy
- Leverages/integrates existing local, state, national assets (e.g. teaching materials, best practice guidelines) and solutions (e.g locally available foods, recipes, resources, etc)
- Addressing barriers and beliefs, myths (e.g. eating down, transport fears, etc
- Offer training to all health workers, eg. bioethics to ensure equity

Every session is structured to:

- Engage participants with their own assessment of salient health needs and solutions
- Provide new information about relevant indicators for the community, specific illness threats to women and children, and about healthy options and local solutions to adopt
- Provide a sample commodity or referral resource, that can be sustainable through subsequent participant choices
- Provide a self-reflection or self-monitoring opportunity for review in the next session

Final versions of the materials and mode of delivery developed in consultation with:

- PIs and co-PIs
- Other team members
- Selected group of CHWs
- Selected group of women (potential participants).

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_CTRI and ISRCTN_
	2b	All items from the World Health Organization Trial Registration Data Set	____NA_____
Protocol version	3	Date and version identifier	____NA_____
Funding	4	Sources and types of financial, material, and other support	____14_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1, 14_____
	5b	Name and contact information for the trial sponsor	_____14_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____14_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____6, 14_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	7-8
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7-8; 10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8; 12-13

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8-9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9; 10-11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8, 12-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	6
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	6, 9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10-11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	6
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10-11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10-11
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	11
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10-11
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A (separate publication policy within consortium)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A (available on request)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A (available on request)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for a cluster randomised trial evaluating a multi-faceted intervention starting preconceptionally - Early Interventions to Support Trajectories for Healthy Life in India (EINSTEIN). A Healthy Life Trajectories Initiative (HeLTI) Study.

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Secondary Subject Heading:	Public health
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Protocol for a cluster randomised trial evaluating a multi-faceted intervention starting preconceptionally - Early Interventions to Support Trajectories for Healthy Life in India (EINSTEIN). A Healthy Life Trajectories Initiative (HeLTI) Study.

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Key words: Developmental origins of health and disease (DOHaD), Multi-faceted intervention; Pre-conceptional intervention; Non-communicable diseases; India

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ABSTRACT

Introduction: The Healthy Life Trajectories Initiative (HeLTI) is an international consortium comprising four harmonised but independently powered trials to evaluate whether an integrated intervention starting pre-conceptionally will reduce non-communicable disease risk in their children. This paper describes the protocol of the India study.

Methods and analysis: The study set in rural Mysore will recruit ~6000 married women over the age of 18 years. The village-based cluster randomised design has three arms (pre-conception, pregnancy and control; 35 villages per arm). The longitudinal multi-faceted intervention package will be delivered by community health workers and comprise: a) measures to optimise nutrition; b) a group parenting programme integrated with cognitive behavior therapy; c) a lifestyle behavior change intervention to support women to achieve a diverse diet, exclusive breastfeeding for the first 6 months, timely introduction of diverse and nutritious infant weaning foods, and adopt appropriate hygiene measures; and d) the reduction of environmental pollution focusing on indoor air pollution and toxin avoidance.

The primary outcome is adiposity in children at age 5 years, measured by fat mass index. We will report on a host of intermediate and process outcomes. We will collect a range of biospecimens including blood, urine, stool, and saliva from the mothers, as well as umbilical cord blood, placenta and specimens from the offspring.

An intention-to-treat analysis will be adopted to assess the effect of interventions on outcomes. We will also undertake process and economic evaluations to determine scalability and public health translation.

Ethics and dissemination: The study has been approved by the institutional ethics committee of the lead institute. Findings will be published in peer-reviewed journals. We will interact with policy makers at local, national and international agencies to enable translation. We will also share the findings with the participants and local community through community meetings, newsletters and local radio.

Trial registration: ISRCTN20161479

Keywords: Non-communicable disease; Developmental Origins of Health and Disease; Pre-conceptional intervention; Childhood adiposity; Child development, Healthy Life Trajectory Initiative (HeLTI)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study will evaluate, for the first time in India, whether a multi-faceted intervention starting pre-conceptionally and continuing through pregnancy, infancy and early childhood reduces risk factors for non-communicable disease in the offspring.
- The study builds upon 35 years of local work which has resulted in strong community engagement and rapport.
- The process and economic evaluations will help in scalability while the use of local community workers will aid translation.
- Given the long-term nature of the study, unblinding of selected outcomes will occur at the end of each phase to enable interim mechanistic analyses and thereby maximise the study potential.
- Due to the study design, effectiveness of individual components of the intervention cannot be evaluated.

INTRODUCTION

Non-communicable diseases (NCDs) are major causes of death and disability globally[1,2] and are rising rapidly in low- and middle-income countries (LMICs) [1–3]. The rising burden of cardiometabolic disease in LMICs is accompanied by a growing recognition of the burden of mental health disorders. Depression is the leading neuropsychiatric cause of disease burden globally and in LMICs[4], and is projected to be the second leading cause of disease burden by 2020[5].

In India, an estimated 65 million people have diabetes and a further 77 million are pre-diabetic[6,7]. Unchecked, the population with diabetes is expected to reach 109 million by 2035[6]. A review showed that 13% of young people aged 1-16 years in India experience mental health disorders[8]. In later life, ~3.7 million people over 60 years of age have dementia; this number is expected to double by 2030 and triple by 2050[9]. These diseases have significant economic implications; the treatment and related costs amount to INR 19914 (US$398) and INR 43285 ($865) per person per year for diabetes[10] and dementia[11], respectively.

The developmental origins of health and disease (DOHaD) hypothesis suggests that adversity during early life influences adult NCD risk[12,13]. DOHaD research suggests that NCD risk is influenced not only by exposure to the well-known 'load' factors such as adult obesity and physical inactivity, but also by the 'capacity' of key metabolic tissues, which is acquired during early development[14]. It is now well established that low birth weight (LBW), poor infant nutrition, and rapid childhood weight gain and obesity are risk factors for poor health trajectories and development of NCDs in later life[15,16].

Undernutrition (including widespread micronutrient deficiencies) remains a significant problem in India. In children under 5, the prevalence of stunting is ~35%; wasting ~17%; underweight ~33%, and anaemia ~41%[17]. In women aged 15-49 years, 23% are underweight (body mass index, BMI<18.5 kg/m^2) while ~53% are anaemic[18]. These factors are reflected in a high prevalence of LBW (<2500g) in ~21% of the 26 million babies born in India each year[19]. Rates of obesity are also increasing; it is estimated that ~12% of children and ~21% of women of reproductive age are overweight or obese (adult BMI>25 kg/m^2)[18].

Application of DOHaD principles offers a novel approach to tackling NCDs by delivering interventions in an integrated manner across the lifecourse: in adolescent or young women to ensure they approach pregnancy in optimum health; in pregnant women to ensure a healthy pregnancy and safe delivery; and in infancy and childhood to prevent excessive childhood adiposity and promote child development.

The Healthy Life Trajectories Initiative

In this context, the Healthy Life Trajectories Initiative (HeLTI) was launched as a joint initiative between the Canadian Institute of Health Research, the Department of Biotechnology of India, the South African Medical Research Council, the National Science Foundation of China and the World Health Organisation. This programme follows a DOHaD approach, focusing on reducing the long-term risk of NCDs through interventions that target the interaction between environmental factors and genes during pre-conception, conception, fetal life, infancy and early childhood. The HeLTI programme comprises four separate but harmonised randomised controlled trials in India, China), South Africa and Canada. The HeLTI interventions are multi-faceted; the rationale is that previous single intervention trials (e.g. multiple micronutrient supplementation) have shown only modest benefits for pregnancy and child outcomes and that multiple interventions are needed to create impact in populations with multiple environmental and social disadvantages. Previous trials have usually started after confirmation of pregnancy and have therefore missed the important peri-

conceptional and early pregnancy processes of epigenetic change, placentation and organogenesis; starting pre-conceptionally will address these issues.

The HeLTI consortium has a collective governance structure for the management of the trials. The two co-lead PIs of each of the four HeLTI trials form an over-arching Research Committee (RC), with rotating chairpersons, responsible for overall project management and oversight, liaising with working groups and reporting to the HeLTI Council (comprising representatives from all the funders and a WHO secretariat). Working groups, including investigators from all countries chaired by one of the lead PIs, develop harmonised protocols, covering biospecimens, data collection, interventions, cohort management and retention, and data management. Each country project team has a Steering Committee, comprising the two PIs and selected co-PIs, which deals with day to day operations and reports to the RC, as well as liaising with participating institutions and community representatives. The four HeLTI trials have a common Data Monitoring and Safety Committee comprising independent international experts, with representation from the four countries involved. The WHO will monitor the trial conduct.

The India Study

We report the protocol for the Indian study, Early Interventions to Support Trajectories for Healthy Life in India (EINSTEIN) in this paper. Research by our group has shown that part of the increased NCD risk in Indians comes from changes in fetal body composition. The undernourished Indian newborn is typically light and thin (average birth weight 2.7kg) and has a low lean body mass, but is disproportionately adipose (the 'thin-fat' Indian)[20,21]. This phenotype persists through childhood and into adult life, and is associated with diabetes and CVD at relatively low levels of obesity. The effects of early life undernutrition are exacerbated by poor weight gain in infancy and rapid childhood weight gain even in the absence of obesity[22].

We have specifically chosen a rural population where obesity is currently uncommon, but undernutrition is common. This population is representative of a large section of the Indian population where economic transition has started and is likely to benefit most from interventions to improve early development (capacity) as well as those that reduce the post-natal obesogenic effects of transition (load).

METHODS AND ANALYSIS

Our overarching aim is to investigate whether an integrated intervention starting pre-conceptionally and continuing at appropriate points across the lifecourse (pregnancy, infancy and childhood) will reduce childhood adiposity and the risk for NCDs as well as improve measures of child neurodevelopment.

Patient and public involvement

Community participation is key to the success of our programme and we have engaged with the local community including community leaders, village women, village elders and local groups, particularly women's self-help groups. We held engagement meetings at village level to explain the study and clarify any queries people may have. We undertook extensive formative work over a period of ~18 months which included face-to-face meetings and focus group discussions. This work helped to finalise our intervention package and delivery methods, and dissemination plans.

Subjects

Our proposed study will be set in rural Mysore, in HD Kote and Saragur Taluks about 50 km from Mysore city in southern India. The population is characterised by subsistence farming, poor nutritional status, low levels of literacy particularly among women, and limited access to specialist health services. Approximately 25% of women are underweight, 19% are overweight, and 45% are anaemic[23]. Less than 60% of infants are exclusively breast fed for 6 months[24]. Over 60% of children under five are anaemic and less than two-thirds are fully

immunised[23,24]. The prevalence of both stunting and underweight in children under five is ~38%[24]. Sanitation and hygiene facilities are limited and toilets are mostly shared. The local area receives potable water from taps, most commonly from shared taps situated in streets. Borewells are also a common source of water. The population is relatively stable, minimizing loss to follow up. Signs of transition are evident; village shops sell high-energy, high-salt, high-sugar snacks and drinks which are mainly consumed by children and young people. Better transport links have increased access to nearby towns and cities, allowing people to seek employment in small/cottage industries.

We have selected 105 villages based on population size (from ~250 in the area) around our main field site, Vivekananda Memorial Hospital (VMH) in Saragur, and will allocate 35 villages to each group, using a standard computerised randomisation programme. We will include women who are over the age of 18, married, have no children or one child, and are planning to have a child within the next two years. We will particularly focus on newly married women, who have a high likelihood of pregnancy within a year.

Study design

The study is a community-based, cluster-randomised intervention with three arms (preconception, pregnancy and control), with individual villages forming the basis for the cluster. Women in all three arms will be recruited together, pre-conceptionally for baseline measurements. The longitudinal multi-faceted intervention will be delivered by trained community health workers (CHWs), which will allow future scalability.

All participants will receive iron and folic acid tablets during pregnancy as per Indian guidelines. Calcium is routinely prescribed in pregnancy by many obstetricians. We will not interfere with routine care provided by the women's obstetricians. We will liaise with local doctors to ensure that they are aware of the study and the supplements their patients are taking, so that the women do not receive 'excess' micronutrients. All women will also receive menstrual hygiene advice and will be provided with a supply of menstrual pads to promote appropriate hygiene practices.

Intervention details

Group 1 (Preconception arm):

Micronutrient supplementation: Women will receive daily micronutrient supplement tablets from recruitment preconceptionally, throughout pregnancy and during breast feeding. Given the high likelihood of multiple deficiencies, the composition will be based on the WHO/UNICEF/UNU international multiple micronutrient preparation (UNIMMAP).

Lifestyle behavior change support: Women will receive support from CHWs trained in Healthy Conversation Skills (HCS), in group settings. The details of the group work are in Appendix 1. HCS is a communication technique developed at the University of Southampton by our wider team for use by health workers to support behaviour change in socio-economically disadvantaged women[25]. This technique has been translated to LMIC settings; in a recent feasibility study involving our group in South Africa, community health workers have been successfully trained in HCS to support young women to improve their diets and lifestyles. The group work emphasises the role of increasing self-efficacy in promoting behaviour change. It is based on the understanding that providing participants with knowledge alone is not sufficient to change their behaviour unless they are also motivated and empowered to change. The aim will be to promote a diverse diet, achieve a normal body weight, and achieve an adequate intake of micronutrients before and during pregnancy, and while breastfeeding. CHWs will provide support postnatally to encourage exclusive breast feeding for the first 6 months and the timely introduction of diverse and nutritious infant weaning foods. Women will be educated about the importance of using safe water for feeding their infants after six months, and advised to use boiled and cooled water. They will receive support to ensure that their infants are fully vaccinated, and that they adopt appropriate hygiene measures, particularly hand washing after using the toilet, changing 'nappies', and before preparing food, eating and feeding their infants. During the pre-conception stage, the group work

will be held at approximately monthly intervals. There will be six modules, with the first module serving as an introductory and general health module. This will be delivered first to all women in the arm. The other five modules will be delivered cyclically and address diet, physical activity and sleep, environmental exposure and hygiene, mental health, and preparing for pregnancy.

Group parenting and cognitive behaviour intervention (Learning Through Play Plus {LTP Plus}): LTP Plus is a group parenting programme, integrated with a cognitive behaviour therapy intervention (Thinking Healthy Programme) designed to address perinatal depression and improve child development in LMIC settings[26,27]. It is a manual assisted, low-literacy, potentially sustainable programme whose activities enhance children's development. It simultaneously promotes attachment security through building parents' ability to be sensitive to their children's cues, and be actively involved in their children's development. These sessions will be delivered in phases which will not only match the woman's pace, but also the gestational period antenatally and the infant's developmental stages postnatally. This two-pronged psychosocial participatory group intervention will help mothers to cope with stress, reduce depression and provide information and strategies that they need to nurture their children's health and development. This will consist of a total of ten sessions, three during pregnancy and seven postnatally. LTP Plus uses a standardized manual and the material will be delivered by CHWs.

Avoiding environmental pollution: We will provide advice and information on avoidance of environmental pollutants particularly indoor smoke (cooking and smoking). We will facilitate LPG (liquefied petroleum gas) connections actively through a recently introduced government scheme which provides subsidized stoves and fuel. We will also address exposure to, and safe handling of pesticides.

Group 2 (Pregnancy arm):
Women in this group will receive the same package of interventions described above, but starting only after they become pregnant, which, in practice, will mean late in the first trimester. Last menstrual period dates will be monitored monthly and women will be offered a urine pregnancy test when they report missing two consecutive periods.

Group 3 (Control arm):
Women in this group will receive an enhanced standard of care. In addition to encouraging vaccinations (two doses of tetanus toxoid) during pregnancy, provision of 100 tablets of iron and folate, and promoting institutional delivery, they will have a similar number of contact sessions with CHWs untrained in our behaviour change and parenting interventions. They will receive standard advice on healthy lifestyle during pregnancy and postnatally, supported by information leaflets (mainly pictorial and using simple language); these will include advice on breastfeeding, immunizations, and infant weaning foods.

Outcomes and assessments
The primary outcome at age 5 years in the children (across all HeLTI cohorts) is adiposity as measured by fat mass index (fat mass/height^2), using DXA (dual x-ray absorptiometry). Other key outcomes at 5-6 years in the children include:

- Overweight and obesity (OWO) as assessed by BMI and indicators of body composition and distribution (waist circumference, skinfold thickness)
- Glucose metabolism as measured by fasting venous plasma glucose concentration
- Resting systolic blood pressure
- Child development as assessed using modified Kaufman battery, validated for Indian settings.

Baseline data on all participants as well as data throughout the study at intervals will be collected (Table 1). Additional phenotypic data will be collected in a subset (ranging between 50-200

individuals per arm, depending on the assessment).

Sample size and power

All the HeLTI studies have calculated their sample size using a minimum power of 80% at 5% significance level to detect a 0.25 standard deviation (SD) difference in offspring fat mass index at 5 years of age between intervention and control groups. We intend to recruit ~6000 initially at baseline. We anticipate 50% will become pregnant within two years (based on data from our formative work). Allowing a 5% pregnancy loss and 20% drop out/loss to follow-up rate, we will have ~750 children in each arm available for follow up to assess our primary outcome (~22 per per village). Assuming an intra-cluster correlation of 0.03, this gives ~95% power to detect a 0.25 SD difference in fat mass between the intervention and control groups and ~80% power to detect sex differences. If pregnancy rates are lower than expected, we will undertake a second round of recruitment at the end of the first year.

Data analysis

As the main outcomes for the study are fat mass index, OWO rate, resting blood pressure, fasting glucose and neurodevelopmental outcomes at age 5 years, and as most children will achieve these ages only in cycle 2 (5-10 years of project), analyses at the end of cycle 1 (0-5 years of project) will explore the effects of the intervention on child anthropometric measures (at birth and serially) and neurodevelopmental outcomes. We will also assess effects on maternal anthropometry, mental health, behavioural risk factors for adiposity/obesity and glycemia. Process indicators including recruitment, retention, and indicators of programme delivery in the intervention group/s will also be determined.

An intention-to-treat analysis will be used for the key outcomes, based on all viable pregnancies. Analysts will be blinded to the study groups. Unblinding will occur after analysis or on the advice of the independent Data Monitoring Committee. We will use mixed models with a cluster-specific approach and robust error estimators adjusted for prespecified potential risk factors related to individual clusters and subjects (such as, locality and level of care, maternal age, parity, pregnancy complications, smoking, and socioeconomic status). First, standard data screening/cleaning procedures will be conducted including the extent and pattern of missing data. We will assess the comparability at randomization of the treatment groups using descriptive analyses. The distribution of modifiable risk factors for childhood obesity, poor cardiometabolic and neurodevelopmental outcomes at baseline, and their changes over time will be assessed according to study group. For women in the intervention groups, we will evaluate the number of scheduled intervention visits, and compliance with micronutrient supplements and attendance at group sessions.

At the end of the 1st cycle of the project, we expect the youngest children to be 1 year of age. We will evaluate the impact of the intervention on all indicators of potential risk factors including weight-for-length at 1 year, birthweight and proportions of SGA/LGA, head and abdominal circumferences at birth and 1 year of age, as well as on indicators of perinatal morbidity/mortality. We will also assess the impact of the intervention on maternal gestational weight gain, the proportion meeting international gestational weight gain guidelines, breastfeeding status as well as on maternal diet and physical activity in the preconception and pregnancy periods.

At 5 years of age in the children, we will assess the effect of the intervention on fat mass index (the primary outcome). Other anthropometric outcomes to be assessed at this time include OWO, BMI and centiles and adiposity (skinfold thickness, arm circumference). We will also assess the effect of the intervention on glucose metabolism, blood pressure and neurodevelopmental outcomes.

Mixed models with random intercept/slope effects and fixed effects (for the intervention) will be used to estimate the intervention effect. Due to possible heterogeneity of effects for key

outcomes according to the time of initiation of the intervention (e.g. preconception versus pregnancy) we will conduct a subgroup analysis stratifying by this variable, testing for heterogeneity. For a 'per-protocol' analysis, we will categorize clusters as high or low according to the compliance with implementation of the intervention. Sensitivity analyses will be performed to assess the influence of losses to follow-up. We will use data on all participants (i.e. with viable pregnancies at inclusion) through multiple imputation.

Economic evaluation: We will undertake cost-effectiveness analysis, from a healthcare payer perspective. We will collect data related to healthcare resource use during the study, including costs of the intervention, CHWs' time, and healthcare use during pregnancy, delivery and infant/child care. Unit costs will be estimated using the activity-based costing method. Our measure of effectiveness will be based on our primary outcome; we will estimate the relative cost-effectiveness of the pre-conception strategy, pregnancy strategy and standard care; an incremental analysis will be conducted comparing the three strategies.

Process evaluation: Evaluation will focus on implementation, mechanisms of impact, and context. Assessment of implementation will focus on determining what is delivered and how delivery is achieved. We will measure fidelity of intervention delivery by observing CHWs in their contacts with intervention group participants, focusing on their use of HCS and LTP Plus and the competencies they demonstrate. We will also observe the contact between CHWs and control participants to record the nature of interactions. We will monitor intervention dose by recording the frequency and duration of contact between participants and CHWs. To understand the mechanisms through which the intervention brings about change in our specified outcomes, we will assess the acceptability of the intervention, and women's experiences of contact with CHWs using interviews and focus groups. In assessing context, we will aim to identify any factor that might act as a barrier or facilitator to intervention implementation or effects. This will include local and national policy, local service configuration and provision, socio-demographic and environmental factors within the villages taking part in the trial, and consultation with key stakeholders. We will also survey non-respondents and those who drop out to gain an understanding of why they did not consent to take part in the study or dropped out during the course of the trial.

Expected outcomes:
The study will provide robust evidence whether an integrated multi-faceted intervention starting pre-conceptionally and continuing through pregnancy and postnatally reduces risk factors for NCD in the offspring. The use of culturally-appropriate interventions will allow scalability if successful. The process and economic evaluations will aid in assessment of translation potential. We will also be able to assess the relative costs and benefits of starting interventions pre-conceptionally versus starting in pregnancy. The study will generate extensive data and build a biorepository which can be used by other researchers within India and elsewhere.

ETHICS AND DISSEMINATION

Ethics approval
The study has been approved by the CSI Holdsworth Memorial Hospital Ethics Committee, (Ref CSIHMH/ERU2019/1). Any protocol modifications will be reported to the committee and approval will be sought for any significant amendments. Informed consent will be obtained from all participants. The families will be given verbal information initially followed by written information in Kannada (local language). The participants will be encouraged to ask questions before obtaining written consent. It will be made clear that they are free to withdraw at any time from the study.

Anonymity and/or confidentiality

Every precaution will be taken to respect the privacy of the women and the confidentiality of their information. We follow research governance practice in accordance with Indian and international guidelines. All data are coded and anonymised before analysis. Strict confidentiality is maintained throughout; hard copy data are stored in locked filing cabinets and in locked rooms, with limited access. Digital data are stored on password-protected encrypted computers, with access only by authorised members of the research team. Biological samples are stored in locked freezers in a secure facility.

Potential risks/harm to participants in the study

None of the interventions or investigations present risks to the participants. Micronutrient supplements have been previously used in community trials and are recommended in the Lancet series on Maternal and Child Nutrition[28] and in the 2015 Cochrane Review on micronutrient supplementation in pregnancy[29]. While we do not expect any adverse effects due to the supplements, the participants will be monitored for adverse events. The LTP Plus programme has been used previously in various LMIC settings and has been shown to reduce maternal depression; there have been no reported adverse outcomes. HCS have also been used previously in community settings without any adverse outcomes. Serious adverse events will be investigated by a medical doctor and reported to the PI and local Co-PIs. Reports will also be submitted to the local institutional ethics committee and the sponsor. Data on adverse events will also be submitted to the independent Data Monitoring Committee. All tests are done under medical supervision and appropriate referral arrangements are in place for issues requiring medical attention.

Dissemination

Participants will receive reports of the relevant physical and biological measurements. If there are any abnormal results, participants will be referred to appropriate medical specialists in VMH for further management and advice.

To maximise the scientific impact, we will engage with the scientific community by presenting our work at major national and international conferences, and by publishing in high-quality peer-reviewed journals, ensuring open access. We will engage with other research groups working on maternal and child health, and develop collaborative opportunities even beyond the duration of the project. Our data will be available to the scientific community after we publish our main findings.

We also will interact with policy makers at local, national and international health agencies, and governments to enable translation of our findings into policy. Members of our collaborative group are linked into national and international policy advisory groups including local, state and national governmental committees in India and Canada, the WHO and Unicef, and we will ensure relevant findings are disseminated through these groups to influence policy. We have met with local health and government officials in the district councils to discuss the public health importance of our study. Their support will be invaluable in future translation. Research findings will be translated into project summaries and policy briefs that capture the major findings and suggest practical policy changes, based on the evidence provided by the project. Recommendations to policy makers will also focus on cost-effectiveness. These documents will be published in English as well as local languages.

The results have implications for all mothers and children, and we will engage with our communities, the wider public, and the mass media. VMH runs a radio station and we will use broadcasts to engage with the local community and provide information and updates. VMH is also actively engaged with local women's self-help groups; we will interact with them throughout the project to not only provide updates of the project, but also to incorporate their feedback into the conduct of the study. We will explain the relevance of our research to our participants and feedback important results to them through six-monthly newsletters and

also by community meetings on an annual basis. We will also publicise the study on our institutional websites and use mass media to ensure that our research findings reach a wide public audience.

In summary, our study will determine whether a longitudinal integrated intervention starting pre-conceptionally improves cardiometabolic and neurodevelopmental outcomes in the next generation. The results will have significant public health implications which can be generalised to other similar settings. The range of biospecimens being collected will allow us to understand causal mechanisms.

Table 1: List of assessments to be carried out at various time points

Mothers	**Baseline**
Physical health	Anthropometry: weight, height; Body composition: Bioimpedance, skinfolds (subset), DXA (subset), stable isotope (subset); Blood pressure: Digital sphygmomanometer
Biospecimen	Blood sample: Plasma, serum, DNA, RNA (subset)
Questionnaires	Diet: Food frequency questionnaire (FFQ), 24-hour food recall, diet diversity and food security questionnaires; Physical activity: Global Physical Activity Questionnaire (GPAQ); Sleep: Pittsburgh Sleep Quality Index (PSQI); General Self Efficacy Scale (GSES); Generalised Anxiety Disorder-7 (GAD-7); Patient Health Questionnaire -9 (PHQ-9); Adverse Childhood Experience (ACE) questionnaire Sociodemography; Socioeconomic status (Standard of Living Index; SLI); Medical/ treatment/drug history; Smoking and alcohol history
	Pregnancy
Physical health	Anthropometry: weight; Body composition: Bioimpedance, stable isotope (subset); Blood pressure: Digital sphygmomanometer
Biospecimen	Blood: Oral glucose tolerance test (OGTT), plasma, serum, DNA, RNA (subset); Urine; Saliva (subset)
Questionnaires	FFQ, 24-hour food recall, diet diversity and food security; GPAQ; PSQI; GSES; GAD-7; Edinburgh Postnatal Depression Scale (EPDS); Social Provision Scale; Breast-feeding Self-efficacy Scale; Perceived Stress Scale Sociodemography; Socioeconomic status (SLI); Medical/ treatment/drug history; Smoking and alcohol history
	Delivery
	Weight; Stool/rectal swab (subset); Delivery details
	Serial postnatal follow-up (up to 60 months)
Physical health	Anthropometry: Weight; Body composition: DXA (subset), stable isotope (subset); Blood pressure: Digital sphygmomanometer; OGTT; blood samples
Biospecimen	Blood: plasma, serum, DNA, RNA (subset), OGTT
Questionnaires	FFQ; 24-hour food recall, diet diversity and food security; GPAQ; PSQI; GSES; GAD-7; EPDS; PHQ-9; Social Provision Scale; Breast-feeding Self efficacy Scale; Perceived Stress Scale; Parenting Stress Index; Sociodemography; Socioeconomic status (SLI); Medical/ treatment/drug history; Smoking and alcohol history
Fathers	**Index pregnancy**
	Anthropometry: Weight, height; Body composition: Bioimpedance, DXA (subset); Blood pressure: Digital sphygmomanometer Blood: Plasma, serum, DNA, RNA (subset), saliva (subset) FFQ; 24-hour food recall, diet diversity and food security; GPAQ; PSQI; PHQ-9 Sociodemography, Socioeconomic status (SLI); Medical/ treatment/drug history; Smoking and alcohol history
Child	**Birth**
	Anthropometry: Weight, length, head/arm/abdomen/chest circumference, skinfolds DXA, Cord blood; Placenta; Umbilical cord; Meconium
	Birth to 12 months
	Anthropometry: Weight, length, circumferences; Body composition: DXA, stable isotope (subset) Feeding history; Vaccination history; Medical/treatment/drug history Stool
	Serial postnatal follow-up (major follow-up at 24 and 60 months)

	Anthropometry: Weight, length/height, circumferences; Body composition: DXA, Blood pressure; Blood samples (heel prick at 24 months and venous sample at 60 months): Plasma, serum, DNA, RNA, glycaemia Feeding history; Sleep Questionnaire; Ages and stages questionnaire; Neuro-cognitive developmental tools: Developmental Assessment *Scale* for Indian Infants (DASII) at 24 months; modified Kaufmann Battery at 60 months; Executive function assessment tools; Physical activity (questionnaire and accelerometry); Screen time questionnaire; General health assessment; Vaccination history; Medical/treatment/drug history

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Competing interests statement: None of the authors declare any conflict of interest. The HeLTI Council of funders and WHO have required all Principal Investigators to complete annual Declarations of Interest and to commit to having no direct or indirect relations with the tobacco, arms and infant food industries during the course of the study.

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Data sharing and access: Data sharing and access arrangements are included in the overall HeLTI governance document. The HeLTI consortium is in the process of establishing a Data Access Portal though which investigators can view and request access to data/biospecimens within individual HeLTI country or multiple country datasets. Data access will follow country-specific guidelines and is expected to require submission of a detailed research plan (including study rationale, hypothesis, analytic methodologies and funding support to complete the study/analyses). Once the study is completed the researchers will be required to submit all analytical and derived data with metadata to be integrated into the HeLTI country datasets, so that it is available to other researchers.

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Appendix 1: HeLTI India (EINSTEIN) Group Work Principles

Intended beneficiaries: Community health workers (CHWs), based at Vivekananda Memorial Hospital will facilitate a series of peer group discussion and learning sessions among all women enrolled into the intervention arms, i.e. the pre-conception and pregnancy arms (and no peer support intervention will be delivered to participants allocated to the control arm).

Components: The peer support "package" will consist of:

(i) Sequential facilitation of 6 pre-conceptional, 5 pregnancy and 5 post-natal timed & targeted content modules by trained CHWs
(ii) Training and refresher sessions for CHWs on Healthy conversation skills (HCS), Learning Through Play Plus (LTP+), and intervention modules facilitation, conducted by trainers from CSI Holdsworth Memorial Hospital
(iii) Regular observation and supportive supervision of CHWs by Quality Control teams and field supervisors/manager.

Materials: Participants each receive a *personalized* pictorial resource/work booklet for the whole set of sessions.

CHW will receive resource guides, attendance and delivery log sheets, and reflection report guides.

Logistics: Peer support groups will be convened in groups of up to 10-12, for delivery each month. In each intervention village/cluster there may be ~30 women enrolled at the beginning, so there will be multiple peer groups per cluster. As more women are enrolled as they become eligible, the groups may increase. After enrollment and baseline data collection (including biospecimens), the initial session will be conducted by a CHW ~2-4 weeks later. Subsequent sessions will be conducted on a "timed and targeted" schedule roughly every month.

Rationale and process of development: The primary topics and specific content mix for each session were developed based on:

- Context of existing services, if any
- Alignment with key goals of the study
- Prioritisation of women's health needs, identified with key stakeholder consultations
- Feedback from initial community engagements (e.g. people recognised that they won't benefit and changes won't be immediate, will benefit future generations, their children).

Spillover chances/potential contamination, although possible, are considered low because of the:

- Individual nature of intervention (including booklet materials being personalized)
- Peers support group discussions are private, small-scale

- Limited social media.

Guiding principles of the peer group sessions:

- Empowering women participants
- Timed and targeted to reproductive stage
- Integrated with HCS approach
- Topical mix packaged unconventionally, but coherently from participant perspectives
- Ground-truthed, using formative research and pre-testing
- Cyclicity, with short enough amplitude for re-exposure during a pregnancy
- Leverages/integrates existing local, state, national assets (e.g. teaching materials, best practice guidelines) and solutions (e.g locally available foods, recipes, resources, etc)
- Addressing barriers and beliefs, myths (e.g. eating down, transport fears, etc
- Offer training to all health workers, eg. bioethics to ensure equity

Every session is structured to:

- Engage participants with their own assessment of salient health needs and solutions
- Provide new information about relevant indicators for the community, specific illness threats to women and children, and about healthy options and local solutions to adopt
- Provide a sample commodity or referral resource, that can be sustainable through subsequent participant choices
- Provide a self-reflection or self-monitoring opportunity for review in the next session

Final versions of the materials and mode of delivery developed in consultation with:

- PIs and co-PIs
- Other team members
- Selected group of CHWs
- Selected group of women (potential participants).

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_CTRI and ISRCTN_
	2b	All items from the World Health Organization Trial Registration Data Set	____NA_____
Protocol version	3	Date and version identifier	____NA_____
Funding	4	Sources and types of financial, material, and other support	____14_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1, 14_____
	5b	Name and contact information for the trial sponsor	_____14_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____14_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____6, 14_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	7-8
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7-8; 10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8; 12-13

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8-9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9; 10-11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8, 12-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	6
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	6, 9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10-11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	6
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10-11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10-11
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	11
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10-11
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A (separate publication policy within consortium)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A (available on request)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A (available on request)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.